10 January 2012
EMA/CHMP/PhVWP/973945/2011
Patient Health Protection

Monthly report **Issue number: 1112**

Pharmacovigilance Working Party (PhVWP)

December 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its December 2011 plenary meeting on 12-14 December 2011.

Safety concerns

Discussions on non-centrally authorised medicinal products are summarised below in accordance with the PhVWP publication policy. The positions agreed by the PhVWP for non-centrally authorised products form recommendations to Member States. For the publication policy, readers are referred to http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/10/WC500006181.pdf.

The PhVWP also provides advice to the Committee for Medicinal Products for Human Use (CHMP) on centrally authorised products and products subject to ongoing CHMP procedures at the request of the CHMP. For safety updates concerning these products, readers are referred to the meeting highlights from the CHMP published under http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_and_events.jsp&mid=.

Gonatropin-releasing hormone (GnRH) agonists – Risk of depression

Some evidence suggests that gonatropin-releasing hormone (GnRH) agonists are associated with an increased risk of depression, which may be severe, and their product information should be updated consistently across the EU.

Following reports of severe depression including suicide from a Japanese survey and a further epidemiological study in the UK, the PhVWP conducted a review of gonatropin-releasing hormone (GnRH) agonists and the risk of depression. The PhVWP concluded that the risk of depression and mood changes should be mentioned and warnings should be included, in a consistent manner and for

European Medicines Agency
7 Westferry Circus ● Canary Wharf
London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

HMA Management Group
Kevin O'Malley House ● Earlsfort Centre
Earlsfort Terrace ● Dublin 2 ● Ireland
Telephone +353 1 634 3453 **Facsimile** +353 1 661 4764
E-mail hma-ps@imb.ie **Website** www.hma.eu

all indications, in the product information of all medicinal products in the EU containing a GnRH agonist[1] (see Annex 1 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well as practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

HMG-CoA reductase inhibitors – Risk of new onset diabetes

HMG-CoA reductase inhibitors (statins) may increase the risk of new onset diabetes in patients already at risk of developing the disease. Patients at risk need monitoring; however the risk-benefit balance remains clearly positive.

Following the publication of a meta-analysis which reported that therapy with HMG-CoA reductase inhibitors (statins) overall was associated with a slightly increased risk for the development of new onset diabetes (NOD), the PhVWP conducted a review of this risk based on all available data. The PhVWP concluded that HMG-CoA reductase inhibitors may increase the risk of NOD in patients already at risk of developing this disease, but that overall the risk-benefit balance remains clearly positive, given the benefit of HMG-CoA reductase inhibitors in reducing major cardiovascular events. A warning should therefore be included in the product information of all HMG-CoA reductase inhibitors authorised in the EU[2] aiming at monitoring of patients at risk (see Annex 2 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the product information, i.e. the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well as practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

The CHMP will be informed of the PhVWP recommendation with regard to the centrally authorised product PRAVAFENIX, containing pravastatin in combination with fenofibrate (for the latest product information see http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001243/human_med_001429.jsp&mid=WC0b01ac058001d124&murl=menus/medicines/medicines.jsp).

Methotrexate – Risk of overdose due to erroneous daily intake of the weekly dose in rheumatologic and dermatologic indications

Product information for methotrexate for oral use in rheumatologic and dermatologic indications should emphasise that it should be taken once a week and patients should be informed of the risk of overdose due to erroneous daily intake of the intended weekly dose. Key elements for risk minimisation should be consistently reflected in product information across the EU to minimise the risk of inadvertent overdose.

Given that cases of overdose, sometimes fatal, with methotrexate in rheumatologic and dermatologic indications due to erroneous daily instead of weekly intake have been reported in the EU, the PhVWP agreed to review how to further minimise the risk of medication errors. The PhVWP concluded that a simple message emphasising the need for adherence to once weekly intake in rheumatologic and dermatologic indications, and a consistent warning on the risk of overdose should be included in the summaries of product characteristics (SmPCs), the package leaflets (PLs) and the labelling of all methotrexate-containing products for oral use authorised in the EU for these indications. The PhVWP

[1] The active substances included in this review were buserelin, goserelin, histrelin, leuprorelin, nafarelin and triptorelin.
[2] The active substances included in this review were atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

further agreed that the question of whether to maintain the option of dividing the weekly dose should be decided at national level, and that additional risk minimisation measures may likewise be implemented at national level if considered appropriate (see Annex 3 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the SmPCs, PLs and labelling, as well as practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

Montelukast – Risk of psychiatric adverse reactions in children

Psychiatric and behaviour-related adverse reactions have been reported in patients treated with montelukast. The current knowledge in this respect is adequately reflected in the existing EU product information and safety monitoring will continue through routine pharmacovigilance activities.

The PhVWP reviewed a risk management plan (RMP) for montelukast, submitted, as requested, by the originator marketing authorisation holder with regard to psychiatric adverse reactions in children following the assessment of the latest periodic safety update report (PSUR). The PhVWP concluded that the available information on psychiatric and behaviour-related adverse reactions are adequately reflected in the existing EU product information and that routine pharmacovigilance activities are adequate to continue monitoring this issue, for example in the framework of preparation and assessment of PSURs, taking into account future findings from ongoing research in children and adolescents (see Annex 4 for the Summary Assessment Report).

Proton-pump inhibitors – Risk of hypomagnesaemia with long-term use

Proton-pump inhibitors (PPIs) may cause serious hypomagnesaemia and therefore for patients expected to be on prolonged treatment, especially when using other hypomagnesaemia-inducing medicines, healthcare professionals should consider measuring magnesium levels before and periodically during PPI treatment.

Following case reports of serious hypomagnesaemia, the PhVWP conducted a review of this risk in association with proton-pump inhibitors (PPIs)[3] and concluded that the product information of all PPI-containing medicinal products authorised in the EU for long-term use should be updated, in particular to inform patients and healthcare professionals that PPIs may cause serious hypomagnesaemia and that therefore healthcare professionals should consider measuring magnesium levels before and periodically during treatment in patients where long term use is expected, and particularly those who concomitantly take other medicines that may cause hypomagnesaemia. The PhVWP also proposed communication on this safety concern to healthcare professionals at the level of Member States (see Annex 5 for the Summary Assessment Report).

The PhVWP informed the CMDh accordingly. For the final wording to be included in the summaries of product characteristics (SmPCs) and package leaflets (PLs), as well as practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

[3] The active substances included in this review were dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

Guidelines and general matters

Below is a summary of the main discussions on guidelines and other general matters of an organisational, regulatory or methodological nature.

Work Plan for the CHMP Pharmacovigilance Working Party 2012

The PhVWP noted that the CHMP, in November 2011, adopted the PhVWP work plan 2012 submitted by the PhVWP. In 2012, the PhVWP will continue focussing on the implementation of the new legislation (see PhVWP Monthly Report 1009), in addition to their continuous safety monitoring of medicines. For the work plan, interested readers are referred to the EMA website (http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000019.jsp&mid=WC0b01ac0580028d92&jsenabled=true).

CHMP Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for In-vivo Clinical Use

The PhVWP noted the release for public consultation of the draft CHMP Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for In-vivo Clinical Use (EMA/CHMP/BMWP/86289/2010). This guideline was developed by the CHMP Blood Products Working Party (BMWP) with input from the PhVWP. Interested readers are referred to the agency's website (http://www.ema.europa.eu).

Regulatory abbreviations

CHMP – Committee for Medicinal Products for Human Use

CMDh – Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human

EU – European Union

HMA – Heads of Medicines Agencies

PASS – post-authorisation safety study

PhVWP – CHMP Pharmacovigilance Working Party

PL – package leaflet

PSUR – periodic safety update report

RMP – risk management plan

SmPC – summary of product characteristics

Annex 1

Summary Assessment Report of the PhVWP December 2011

Gonatropin-releasing hormone (GnRH) agonists – Risk of depression

Key message

Some evidence suggests that gonatropin-releasing hormone (GnRH) agonists are associated with an increased risk of depression, which may be severe, and their product information should be updated consistently across the EU.

Safety concern and reason for current safety review

An increased risk of depression and depressive symptoms is known in patients treated with gonatropin-releasing hormone (GnRH) agonists and is related to the reduction in oestrogen/testosterone levels.

Following reports of severe depression including suicide from a Japanese survey of women with endometriosis treated with GnRH agonists [1], the marketing authorisation holder of the GnRH agonist leuprorelin performed an epidemiological study in the UK General Practice Research Database (GPRD). The study revealed an increased risk of incident depression in endometriosis and prostate cancer patients treated with GnRH agonists and an increased risk of suicide behaviour in prostate cancer patients treated with GnRH agonists.

The PhVWP agreed to carefully evaluate the new evidence of the increased risk caused by GnRH agonists, considering that depressive symptoms are already common in patients requiring treatment with GnRH agonists.

Clinical setting

Gonatropin-releasing hormone (GnRH) agonists are used for gonadal suppression in various sex hormone-dependent conditions, including prostate cancer, breast cancer and endometriosis.

The GnRH agonists included in this review were buserelin, goserelin, histrelin, leuprorelin, nafarelin and triptorelin.

Patients with prostate cancer being treated with GnRH agonists are known to be at increased risk of developing depression or of a worsening of pre-existing depression. There is also a potential increased risk of mood changes and depression in females treated with GnRH agonists for non-cancer hormone-dependent conditions. Thoughts of death, suicidal ideation and suicide attempts are frequent complications of severe depression.

Information on the data assessed

The data assessed in this review included data from the GPRD study and a previous assessment of the safety of leuprorelin based on a comprehensive review of the relevant literature [1-11] and spontaneous adverse reaction reports. Member States were also requested to provide information on the current product information for all GnRH agonists in their countries.

Outcome of the assessment

The GPRD study showed a rate of incident depression in the range of 1 to 10 cases per 100 person-years in male and female patients with indications for GnRH agonist treatment.

In endometriosis patients, the use of GnRH agonists was associated with around a 50% increase in the risk of incident depression (relative risk (RR): 1.46; 95%CI: 1.12-1.89). The size of this risk overlaps with that seen in unexposed patients (RR 1.38; 95%CI: 1.29-1.48).

In prostate cancer patients, GnRH agonist use was associated with a RR of 1.97 (95%CI: 1.86-2.10) of incident depression. This RR is above that associated with prostate cancer itself (RR 1.45; 95%CI: 1.35-1.55). Similar results were obtained when comparing patients with past exposure to GnRH agonists. An increased risk of suicide behaviour was observed in prostate cancer patients treated with GnRH agonists, but results should be interpreted with caution due to small number of events and potential biases related to the retrospective and observational nature of the study.

The review of literature [2-11] and spontaneous adverse reaction reports revealed that depression and mood changes are known risks related to the reduction of oestrogen/testosterone levels during treatment with GnRH agonists. Responses from the different Member States revealed the need for improved harmonised information on this risk in the product information of the whole class of GnRH agonists.

The PhVWP concluded that the risk of depression and mood changes should be mentioned, in consistent manner and for all indications, in the product information of all medicinal products in the EU containing a GnRH agonist, namely buserelin, goserelin, histrelin, leuprorelin, nafarelin or triptorelin.

The summaries of product characteristics (SmPCs) should include a warning that there is an increased risk of incident depression, which may be severe, in patients undergoing treatment with GnRH agonists and ask that patients are informed accordingly and treated as appropriate if symptoms occur. Also, mood changes and depression should be included in the SmPC section on undesirable effects with the frequency category "common" in long term use and "uncommon" in short term use. Higher frequencies may be appropriate for specific products and indications based on their own clinical trial and other data.

The package leaflets (PLs) should warn the patient that there have been reports of depression, in some cases severe, in patients taking the respective medicinal product and ask the patient to inform a physician in the case of depressed mood. The PL section on possible side effects should be in accordance with the SmPC.

References

[1] Japan Endometriosis Association publishes third national study. April 2007; available under: http://endometriosis.org/news/support-awareness/japan-endometriosis-association-announces-significantly-adverse-effects-of-gnrh-use/ (last accessed 20 Dec 2011).

[2] Cherrier MM, Aubin S, Higano CS. Cognitive and mood changes in men undergoing intermittent combined androgen blockade for non-metastatic prostate cancer. Psychooncology. 2009; 18: 237-247.

[3] Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of the "androgen deprivation syndrome" in men receiving androgen deprivation for prostate cancer. Arch Intern Med. 2006; 166: 465-471.

[4] Schmidt PJ, Berlin KL, Danaceau MA, Neeren A, Haq NA, Roca CA, Rubinow DR. The effects of pharmacologically induced hypogonadism on mood in healthy men. Arch Gen Psychiatry. 2004; 61: 997-1004.

[5] Rosenblatt DE, Mellow A. Depression during hormonal treatment of prostate cancer. J Am Board Fam Pract. 1995; 8: 317-320.

[6] Sepulcri Rde P, do Amaral VF. Depressive symptoms, anxiety, and quality of life in women with pelvic endometriosis. Eur J Obstet Gynecol Reprod Biol. 2009; 142: 53-56.

[7] Steingold KA, Cedars M, Lu JK, Randle D, Judd HL, Meldrum DR. Treatment of endometriosis with a long-acting gonadotropin-releasing hormone agonist. Obstet Gynecol. 1987; 69: 403-411.

[8] Warnock JK, Bundren JC. Anxiety and mood disorders associated with gonadotropin-releasing hormone agonist therapy. Psychopharmacol Bull. 1997; 33: 311-316.

[9] Bloch M, Azem F, Aharonov I, Ben Avi I, Yagil Y, Schreiber S, Amit A, Weizman A. GnRH-agonist induced depressive and anxiety symptoms during in vitro fertilization-embryo transfer cycles. Fertil Steril. 2011; 95: 307-309.

[10] Friedman AJ, Hoffman DI, Comite F, Browneller RW, Miller JD. Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. The Leuprolide Study Group. Obstet Gynecol. 1991; 77: 720-725.

[11] Toren P, Dor J, Mester R, Mozes T, Blumensohn R, Rehavi M, Weizman A. Depression in women treated with a gonadotropin-releasing hormone agonist. Biol Psychiatry. 1996; 39: 378-82.

Annex 2

Summary Assessment Report of the PhVWP December 2011

HMG-CoA reductase inhibitors – Risk of new onset diabetes

Key message

HMG-CoA reductase inhibitors (statins) may increase the risk of new onset diabetes in patients already at risk of developing the disease. Patients at risk need monitoring; however the risk-benefit balance remains clearly positive.

Safety concern and reason for current safety review

Following the publication of a meta-analysis in 2010 [1] which reported that therapy with HMG-CoA reductase inhibitors overall was associated with a slightly increased risk for the development of new onset diabetes (NOD), the PhVWP agreed to conduct a review of this risk based on all the available data, both published and unpublished.

Since the publication of a trial in 2001 (WOSCOPS) [2], a number of clinical trials have examined the association between HMG-CoA reductase inhibitors and NOD. Although WOSCOPS [2] suggested a decreased risk for NOD, the JUPITER [3] and PROSPER [4] studies suggested an increased risk and the recent meta-analysis of 13 trials [1] reported that HMG-CoA reductase inhibitor treatment overall was associated with a slightly increased risk for the development of NOD (odds ratio 1.09; 95% CI 1.02-1.17). The authors calculated that this represented 1 additional case of diabetes per 1,000 person-years of treatment. Alternatively this could be expressed as 1 additional patient developing diabetes, who would not otherwise had done so, for every 255 patients treated for 4 years with a HMG-CoA reductase inhibitor.

Clinical setting

HMG-CoA reductase inhibitors, commonly known as statins, are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) which controls the rate-limiting step in the cholesterol biosynthesis. These active substances are used to lower lipids in the blood.

There are differences between individual HMG-CoA reductase inhibitors in terms of both lipophilicity and potency, which may affect the ability of these substances to influence glucose homeostasis. However the two characteristics are not linked in that rosuvastatin is both hydrophilic and potent, pravastatin is hydrophilic but relatively less potent while atorvastatin is both lipohilic and potent.

HMG-CoA reductase inhibitors are one of the most widely prescribed classes of medicinal products in the EU, and prescribing is continuing to grow. Thus even a relatively small increase in the risk of NOD could potentially result in a significant number of additional cases of diabetes per year.

The active substances included in this review were atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

Information on the data assessed

A list of questions was sent to the originator marketing authorisation holders for the concerned active substances in order to obtain all available data. Both non-clinical and clinical studies were assessed [1-130].

Outcome of the assessment

The non-clinical studies provided important mechanistic information but their clinical relevance is limited by the difficulty in replicating risk factors for diabetes which clinically would develop over many years in animal models.

Comparison across different clinical studies and thus the class of HMG-CoA reductase inhibitors was limited by different patient populations, length of study and dose. As a result, stratification of patient population by risk factors may yield different conclusions to those drawn when considering the patient population as a whole. In addition for the majority of the trials, diabetes was not a predefined end point and therefore the method of diagnosis of diabetes differed between trials varying between physicians reporting only to documented biochemical analysis. Furthermore the frequency and time of analysis differed in that some trials relied on a single measurement of fasting blood glucose while others required two raised levels for the diagnosis of diabetes. Relatively few trials assessed HbA1c levels, a more long term, sensitive measure of glucose homeostasis.

All studies clearly demonstrated that the benefit of HMG-CoA reductase inhibitors in reducing major cardiovascular events is still maintained to a similar extent in patients developing NOD compared with those patients that do not. Set against the increased risk of 1 case of diabetes for every 255 patients treated with a HMG-CoA reductase inhibitors for 4 years, it was estimated that 5.4 deaths or myocardial infarctions could be avoided over that period in addition to the same number of strokes or coronary revascularisations. Hence the benefit in preventing total vascular events is approximately 9:1 in favour of the cardiovascular benefit. Thus the risk-benefit balance of these medicines remains clearly positive, including in those with diabetes or at risk of developing diabetes.

From the analysis of the non-clinical and clinical data, the PhVWP concluded that there is sufficient evidence to support a causal association between use of HMG-CoA reductase inhibitors and NOD. However the risk appears to be predominantly in patients already at increased risk of developing diabetes. Raised fasting blood glucose at baseline is a key factor in determining this increased risk and may be sufficient to delineate the at-risk population. Other risk factors include a history of hypertension, raised triglycerides and raised body mass index at baseline.

The evidence for a causal association is currently weakest for pravastatin where trials have suggested both an increased and decreased risk of NOD associated with therapy. However, given the critical influence the patient population plays in determining the risk of diabetes, there is currently insufficient data to exclude any HMG-CoA reductase inhibitor from the possibility of exacerbating the risk of NOD in a susceptible individual.

Despite the conclusion that the risk of NOD is increased in susceptible individuals, studies clearly demonstrate that the benefit of HMG-CoA reductase inhibitors in reducing major cardiovascular events is still maintained to a similar extent in this population. As a result the risk-benefit balance of these medicines remains clearly positive, including in those at risk of diabetes and with diabetes at baseline. However risk minimisation measures should be introduced in order to specify patients who are at risk, to identify the onset of NOD and to manage the condition appropriately.

Considering the above, the PhVWP concluded that a warning that HMG-CoA reductase inhibitors as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of

hyperglycaemia where formal diabetes care is appropriate should be included in the product information, i.e. the summaries of product characteristics (SmPCs) and the package leaflets, of all HMG-CoA reductase inhibitors authorised in the EU, namely medicinal products containing atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. The warning should state that patients at risk (i.e. those with fasting glucose 5.6 - 6.9 mmol/L, body mass index > 30kg/m^2, raised triglycerides or hypertension) should be monitored both clinically and biochemically according to national guidelines. In the undesirable effect sections of the product information, diabetes mellitus should be included as a common adverse reaction, supplemented in the SmPC with detailed data from the major studies.

References

[1] Sattar N, Preiss D, Murray HM et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010; 375: 735-742.

[2] Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A. Pravastatin and the Development of Diabetes Mellitus: Evidence for a Protective Treatment Effect in the West of Scotland Coronary Prevention Study. Circulation. 2001; 103: 357-362.

[3] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med. 2008; 359: 2195-2207.

[4] Shepherd J, Blauw GJ, Murphy MB et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002; 360: 1623-1630.

[5] Yamazaki M, Suzuki H, Hanano M, Tokui T, Kamai T, Sugiyama Y. Sodium- independent multispecific ion transporter mediates active transport of pravastatin into rat liver. Am J Physiol. 1993; 264: G36-44.

[6] Yada T, Nakata M, Shiraishi T, Kakei M. Inhibition by simvastatin, but not pravastatin, of glucose-induced cytosolic Ca2+ signalling and insulin secretion due to blockade of L-type Ca2+ channels in rat islet beta-cells. Br J Pharmacol. 1999; 126: 1205-1213.

[7] Nakahara K, Yada T, Kuriyama M, Osame M. Cytosolic Ca2+ Increase and Cell Damage in L6 Rat Myoblasts by HMG-CoA Reductase Inhibitors. Biochem Biophys Res Commun. 1994; 202: 1579-1585.

[8] Shepherd J, Hunninghake DB, Barter P, McKenney JM, Hutchinson HG. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. Am J Cardiol. 2003; 91: 11C-17C.

[9] Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005; 19: 117-125.

[10] Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients With Hypercholesterolemia (The CURVES Study). Am J Cardiol. 1998; 81: 582-587.

[11] Zhang L, Zhang S, Jiang H, Sun A, Wang Y, Zou Y, Ge J, Chen H. Effects of statin therapy on inflammatory markers in chronic heart failure: a meta-analysis of randomised controlled trials. Arch Med Res. 2010; 41: 464-471.

[12] Christ M, Bauersachs J, Liebetrau C, Heck M, Gunther A, Wehling M. Glucose increases endothelial-dependent superoxide formation in coronary arteries by NAD(P)H oxidase activation: attenuation by the 3-hydroxy-3- methylglutaryl coenzyme A reductase inhibitor atorvastatin. Diabetes. 2002; 51: 2648-2652.

[13] Su Y, Xu Y, Sun YM, Li J, Liu XM, Li YB, Liu GD, Bi S. Comparison of the Effects of Simvastatin versus Atorvastatin on Oxidative Stress in Patients With Type 2 Diabetes Mellitus. J Cardiovasc Pharmacol. 2010; 55: 21-25.

[14] Vecchione C, Gentile MT, Aretini A, Marino G, Poulet R, Maffei A, Passarelli F, Landolfi A, Vasta A, Lembo G. A novel mechanism of action for statins against diabetes-induced oxidative stress. Diabetologia. 2007; 50: 874-880.

[15] Wang W, Wong CW. Statins enhance peroxisome proliferator-activated receptor gamma coactivator-1alpha activity to regulate energy metabolism. J Mol Med. 2010; 88: 309-317.

[16] Paintlia AS, Paintlia MK, Singh AK, Orak JK, Singh I. Activation of PPAR- gamma and PTEN cascade participates in lovastatin-mediated accelerated differentiation of oligodendrocyte progenitor cells. Glia. 2010; 58: 1669-1685.

[17] Lee J, Hong EM, Koh DH, Choi MH, Jang HJ, Kae SH, Choi HS. HMG-CoA reductase inhibitors (statins) activate expression of PPARalpha/PPARgamma and ABCA1 in cultured gallbladder epithelial cells. Dig Dis Sci. 2010; 55: 292-299.

[18] Pessin JE, Bell GI. Mammalian Facilitative Glucose Transporter Family: Structure and Molecular Regulation. Annu Rev Physiol. 1992; 54: 911-930.

[19] Minokoshi Y, Kahn CR, Kahn BB. Tissue-specific Ablation of the GLUT4 Glucose Transporter or the Insulin Receptor Challenges Assumptions about Insulin Action and Glucose Homeostasis. J Biol Chem. 2003; 278: 33609-33612.

[20] DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP. The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. Diabetes. 1981; 30: 1000-1007.

[21] Basu A, Basu R, Shah P et al. Type 2 Diabetes Impairs Splanchnic Uptake of Glucose but Does Not Alter Intestinal Glucose Absorption During Enteral Glucose Feeding. Diabetes. 2001; 50: 1351-1362.

[22] Abel ED, Peroni O, Kim JK, Kim YB, Boss O, Hadro E, Minnemann T, Shulman GI, Kahn BB. Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver. Nature. 2001; 409: 729-733.

[23] Birnbaum MJ. Diabetes: Dialogue between muscle and fat. Nature. 2001; 409: 672-673.

[24] Carvalho E, Kotani K, Peroni OD, Kahn BB. Adipose-specific overexpression of GLUT4 reverses insulin resistance and diabetes in mice lacking GLUT4 selectively in muscle. Am J Physiol Endocrinol Metab. 2005; 289: E551-E561.

[25] Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Mol Cell Endocrinol. 2010; 316: 129-139.

[26] Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes:a systematic review and meta-analysis. JAMA. 2009; 302: 179-188.

[27] Phillips SA, Kung JT. Mechanisms of adiponectin regulation and use as a pharmacological target. Curr Opin Pharmacol. 2010; 10: 676-683.

[28] Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. Nature. 2001; 409: 307-312.

[29] Patel SD, Rajala MW, Rossetti L, Scherer PE, Shapiro L. Disulfide-dependent multimeric assembly of resistin family hormones. Science. 2004; 304: 1154-1158.

[30] Rajala MW, Qi Y, Patel HR, Takahashi N, Banerjee R, Pajvani UB, Sinha MK, Gingerich RL, Scherer PE, Ahima RS. Regulation of resistin expression and circulating levels in obesity, diabetes, and fasting. Diabetes. 2004; 53: 1671-1679.

[31] Patel L, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, Plumpton C, Macphee CH, Smith SA. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem Biophys Res Commun. 200; 300: 472-476.

[32] Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, Kotani K, Quadro L, Kahn BB. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature. 2005; 436: 356-362.

[33] Berg AH, Scherer PE. Adipose Tissue, Inflammation, and Cardiovascular Disease. Circ Res. 2005; 96: 939-949.

[34] Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab. 2001; 280: E745-E751.

[35] Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis. 2000; 148: 209-214.

[36] Wang Z, Thurmond DC. Mechanisms of biphasic insulin-granule exocytosis - roles of the cytoskeleton, small GTPases and SNARE proteins. J Cell Sci. 2009; 122: 893-903.

[37] Zhou Q, Liao JK. Pleiotropic effects of statins - Basic research and clinical perspectives. Circ J. 2010; 74: 818-826.

[38] Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol. 2005; 45: 89-118.

[39] Hao M, Bogan JS. Cholesterol regulates glucose-stimulated insulin secretion through phosphatidylinositol 4,5-bisphosphate. J Biol Chem. 2009; 284: 29489-29498.

[40] Nakata M, Nagasaka S, Kusaka I, Matsuoka H, Ishibashi S, Yada T. Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control. Diabetologia. 2006; 49: 1881-1892.

[41] Bellosta S, Paoletti R, Corsini A. Safety of Statins: Focus on Clinical Pharmacokinetics and Drug Interactions. Circulation. 2004; 109: III50-57.

[42] Camp HS, Ren D, Leff T. Adipogenesis and fat-cell function in obesity and diabetes. Trends Mol Med. 2002; 8: 442-447.

[43] Mauser W, Perwitz N, Meier B, Fasshauer M, Klein J. Direct adipotropic actions of atorvastatin: Differentiation state-dependent induction of apoptosis, modulation of endocrine function, and inhibition of glucose uptake. Eur J Pharmacol. 2007; 564: 37-46.

[44] Takaguri A, Satoh K, Itagaki M, Tokumitsu Y, Ichihara K. Effects of atorvastatin and pravastatin on signal transduction related to glucose uptake in 3T3L1 adipocytes. J Pharmacol Sci. 2008; 107: 80-89.

[45] Chamberlain LH. Inhibition of isoprenoid biosynthesis causes insulin resistance in 3T3-L1 adipocytes. FEBS Letters. 2001; 507: 357-361.

[46] Nicholson AC, Hajjar DP, Zhou X, He W, Gotto AM, Han J. Anti-adipogenic action of pitavastatin occurs through the coordinate regulation of PPAR+¦ and Pref-1 expression. Br J Pharmacol. 2007; 151: 807-815.

[47] Chan KC, Wang CJ, Ho HH, Chen HM, Huang CN. Simvastatin inhibits cell cycle progression in glucose-stimulated proliferation of aortic vascular smooth muscle cells by up-regulating cyclin dependent kinase inhibitors and p53. Pharmacol Res. 2008; 58(3-4): 247-256.

[48] Takano T, Yamakawa T, Takahashi M, Kimura M, Okamura A. Influences of statins on glucose tolerance in patients with type 2 diabetes mellitus. J Atheroscler Thromb. 2006; 13: 95-100.

[49] Khan T, Hamilton MP, Mundy DI, Chua SC, Scherer PE. Impact of Simvastatin on Adipose Tissue: Pleiotropic Effects in Vivo. Endocrinology. 2009; 150: 5262-5272.

[50] Chen Y, Ohmori K, Mizukawa M, Yoshida J, Zeng Y, Zhang L, Shinomiya K, Kosaka H, Kohno M. Differential impact of atorvastatin vs pravastatin on progressive insulin resistance and left ventricular diastolic dysfunction in a rat model of type II diabetes. Circ J. 2007; 71: 144-152.

[51] Wong V, Stavar L, Szeto L, Uffelman K, Wang CH, Fantus IG, Lewis GF. Atorvastatin induces insulin sensitization in Zucker lean and fatty rats. Atherosclerosis. 2006: 184: 348-355.

[52] Suzuki M, Kakuta H, Takahashi A, Shimano H, Tada-Iida K, Yokoo T, Kihara R, Yamada N. Effects of atorvastatin on glucose metabolism and insulin resistance in KK/Ay mice. J Atheroscler Thromb. 2005; 12: 77-84.

[53] Mangaloglu L, Cheung RC, Van Iderstine SC, Taghibiglou C, Pontrelli L, Adeli K. Treatment with atorvastatin ameliorates hepatic very-low-density lipoprotein overproduction in an animal model of insulin resistance, the fructose-fed Syrian golden hamster: evidence that reduced hypertriglyceridemia is accompanied by improved hepatic insulin sensitivity. Metabolism. 2002; 51: 409-418.

[54] Naples M, Federico LM, Xu E, Nelken J, Adeli K. Effect of rosuvastatin on insulin sensitivity in an animal model of insulin resistance: Evidence for statin- induced hepatic insulin sensitization. Atherosclerosis. 2008; 198: 94-103.

[55] Furuya DT, Poletto AC, Favaro RR, Martins JO, Zorn TMT, Machado UF. Anti-inflammatory effect of atorvastatin ameliorates insulin resistance in monosodium glutamate-treated obesemice. Metabolism. 2010; 59: 395-399.

[56] Otani M, Yamamoto M, Harada M, Otsuki M. Effect of long- and short-term treatments with pravastatin on diabetes mellitus and pancreatic fibrosis in the Otsuka-Long-Evans-Tokushima fatty rat. Br J Pharmacol. 2010; 159: 462-473.

[57] Satoh K, Keimatsu N, Kanda M, Kasai T, Takaguri A, Sun F, Ichihara K. HMG-CoA reductase inhibitors do not improve glucose intolerance in spontaneously diabetic Goto-Kakizaki rats. Biol Pharm Bull. 2005; 28: 2092-2095.

[58] Lacraz Gg, Figeac F, Movassat J, Kassis N, Portha B. Diabetic GK/Par rat +¦- cells are spontaneously protected against H2O2-triggered apoptosis. A cAMP-dependent adaptive response. Am J Physiol Endocrinol Metab. 2010; 298: E17-E27.

[59] Barter P, McPherson YR, Song K, Kesäniemi YA, Mahley R, Waeber G, Bersot T, Mooser V, Waterworth D, Grundy SM. Serum insulin and inflammatory markers in overweight individuals with and without dyslipidemia. J Clin Endocrinol Metab. 2007; 92: 2041-2045.

[60] Stirnadel H, Lin X, Ling H, Song K, Barter P, Kesäniemi YA, Mahley R, McPherson R, Waeber G, Bersot T, Cohen J, Grundy S, Mitchell B, Mooser V, Waterworth D. Genetic and phenotypic architecture of metabolic syndrome-associated components in dyslipidemic and normolipidemic subjects: the GEMS Study. Atherosclerosis. 2008; 197: 868-876.

[61] Shand BI, Scott RS, Lewis JG, Elder PA, Frampton CM. Comparison of indices of insulin resistance with metabolic syndrome classifications to predict the development of impaired fasting glucose in overweight and obese subjects: a 3-year prospective study. Int J Obes (Lond). 2009; 33: 1274-1279.

[62] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet. 2005; 366: 1267-1278.

[63] Cannon CP. Balancing the benefits of statins versus a new risk-diabetes. Lancet. 2010; 375: 700-701.

[64] Ando H, Sugimoto K, Yanagihara H, Tsuruoka S, Saito T, Takamura T, Kaneko S, Fujimura A. Effects of atorvastatin and pravastatin on glucose tolerance, adipokine levels and inflammatory markers in hypercholesterolaemic patients. Clin Exp Pharmacol Physiol. 2008; 35: 1012-1017.

[65] Sabatine MS, Wiviott SD, Morrow DA, McCabe CH, Cannon CP. High dose atorvastatin associated with worse glycemic control: A PROVE-IT TIMI 22 substudy. Circulation. 2004; 110 (SIII): 834.

[66] Waters DD, Ho JE, DeMicco DA, Breazna A, Arsenault BJ, Wun CC, Kastelein JJ, Colhoun H, Barter P. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. J Am Coll Cardiol. 2011; 57: 1535-1545.

[67] Bonnet J, McPherson R, Tedgui A, Simoneau D, Nozza A, Martineau P, Davignon J; CAP Investigators. Comparative effects of 10-mg versus 80-mg atorvastatin on high-sensitivity C-reactive protein in patients with stable coronary artery disease: results of the CAP (Comparative Atorvastatin Pleiotropic effects) study. Clin Ther. 2008; 30: 2298-2313.

[68] Ding PY-A, Hsu P-F, Lu T-M. Statin therapy on insulin resistance and plasma level of adiponectin in non-diabetic, hypercholesterolemic patients. Acta Cardiol Sin. 2009; 25: 183-189.

[69] Costa A, Casamitjana R, Casals E, Alvarez L, Morales J, Masramón X, Hernández G, Gomis R, Conget I. Effects of atorvastatin on glucose homeostasis, postprandial triglyceride response and C-reactive protein in subjects with impaired fasting glucose. Diabet Med. 2003; 20: 743-745.

[70] Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Shin EK. Atorvastatin Causes Insulin Resistance and Increases Ambient Glycemia in Hypercholesterolemic Patients. J Am Coll Cardiol. 2010; 55: 1209-1216.

[71] Thongtang N, Ai M, Otokozawa S, Himbergen TV, Asztalos BF, Nakajima K, Stein E, Jones PH, Schaefer EJ. Effects of maximal atorvastatin and rosuvastatin treatment on markers of glucose homeostasis and inflammation. Am J Cardiol. 2011; 107: 387-392.

[72] Her AY, Kim JY, Kang SM Choi D, Jang Y, Chung N, Manabe I, Lee SH. Effects of atorvastatin 20 mg, rosuvastatin 10 mg, and atorvastatin/ezetimibe 5 mg/5 mg on lipoproteins and glucose metabolism. J Cardiovasc Pharmacol Ther. 2010; 15: 167-174.

[73] Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003; 361: 1149-1158.

[74] Hoenig MR, Sellke FW. Insulin resistance is associated with increased cholesterol synthesis, decreased cholesterol absorption and enhanced lipid response to statin therapy. Atherosclerosis. 2010; 211: 260-265.

[75] Ohmura C, Watada H, Hirose T, Tanaka Y, Kawamori R. Acute onset and worsening of diabetes concurrent with administration of statins. Endocr J. 2005; 52: 369-372.

[76] Krysiak R, Gdula-Dymek A, Bachowski R, Okopien B. Pleiotropic effects of atorvastatin and fenofibrate in metabolic syndrome and different types of pre-diabetes. Diabetes Care. 2010; 33: 2266-2270.

[77] Mita T, Watada H, Nakayama S, Abe M, Ogihara T, Shimizu T, Uchino H, Hirose T, Kawamori R. Preferable effect of pravastatin compared to atorvastatin on beta cell function in Japanese early-state type 2 diabetes with hypercholesterolemia. Endocr J. 2007; 54: 441-447.

[78] Tanaka A, Yamada N, Saito Y, Kawakami M, Ohashi Y, Akanuma Y. A double-blind trial on the effects of atorvastatin on glycemic control in Japanese diabetic patients with hypercholesterolemia. Clin Chim Acta. 2001; 312: 41-47.

[79] Ceriello A, Assaloni R, Da Ros R, Maier A, Piconi L, Quagliaro L, Esposito K, Giugliano D. Effect of atorvastatin and irbesartan, alone and in combination, on postprandial endothelial dysfunction, oxidative stress, and inflammation in type 2 diabetic patients. Circulation. 2005; 111: 2518-2524.

[80] Pedersen TR, Faergeman O, Kastelein JJ et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005; 294: 2437-2445.

[81] Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE, Callahan A 3rd, Hennerici M, Simunovic L, Zivin JA, Welch KM; SPARCL Investigators. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke. 2007; 38: 3198-3204.

[82] LaRosa JC, Deedwania PC, Shepherd J, Wenger NK, Greten H, DeMicco DA, Breazna A; TNT Investigators. Comparison of 80 versus 10 mg of atorvastatin on occurrence of cardiovascular events after the first event (from the Treating to New Targets [TNT] trial). Am J Cardiol. 2010; 105: 283-287.

[83] Avignon A, Radauceanu A, Monnier L. Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetics. Diabetes Care. 1997; 20: 1822-1826.

[84] Ishikawa M, Namiki A, Kubota T Yajima S, Fukazawa M, Moroi M, Sugi K. Effect of pravastatin and atorvastatin on glucose metabolism in nondiabetic patients with hypercholesterolemia. Intern Med. 2006; 45: 51-55.

[85] Pihlajamaki J, Gylling H, Miettinen TA, Laakso M. Insulin resistance is associated with increased cholesterol synthesis and decreased cholesterol absorption in normoglycemic men. J Lipid Res. 2004; 45: 507-512.

[86] Gylling H, Hallikainen M, Pihlajamaki J Simonen P, Kuusisto J, Laakso M, Miettinen TA. Insulin sensitivity regulates cholesterol metabolism to a greater extent than obesity: lessons from the METSIM Study. J Lipid Res. 2010; 51: 2422-2427.

[87] Gylling H, Hallikainen M, Kolehmainen M, Toppinen L, Pihlajamäki J, Mykkänen H, Agren JJ, Rauramaa R, Laakso M, Miettinen TA. Cholesterol synthesis prevails over absorption in metabolic syndrome. Trans Res. 2007; 149: 310-316.

[88] Angelin B, Backman L, Einarsson K, Eriksson L, Ewerth S. Hepatic cholesterol metabolism in obesity: activity of microsomal 3-hydroxy-3- methylglutaryl coenzyme A reductase. J Lipid Res. 1982; 23: 770-773.

[89] Kappagoda CT, Amsterdam EA. Another Look at the results of the JUPITER Trial. Am J Cardiol. 2009; 104: 1603-1605.

[90] Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, Grobbee DE, Bots ML; METEOR Study Group. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR trial. JAMA. 2007; 297: 1344-1353.

[91] Kjekshus J, Apetrei E, Barrios V et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med. 2007; 357: 2248-2261.

[92] Fellström BC, Jardine AG, Schmieder RE et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009; 360: 1395-1407.

[93] Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008; 372: 1231-1239.

[94] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994; 344: 1383-1389.

[95] de Lemos JA, Blazing MA, Wiviott SD et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004; 292: 1307-1316.

[96] Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003; 361: 2005-2016.

[97] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo controlled trial. Lancet. 2002; 360: 7-22.

[98] Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Peto R, Collins R. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12[punctuation space]064 survivors of myocardial infarction: a double-blind randomised trial. Lancet. 2010; 376: 1658-1669.

[99] Devaraj S, Siegel D, Jialal I. Simvastatin (40 mg/day), adiponectin levels, and insulin sensitivity in subjects with the metabolic syndrome. Am J Cardiol. 2007; 100: 1397-1399.

[100] Holdaas H, Fellström B, Jardine AG et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo- controlled trial. Lancet. 2003; 361: 2024-2031.

[101] Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, Branzi A, Bertolami MC, Jackson G, Strauss B, Meier B; Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention. JAMA. 2002; 287: 3215-3222.

[102] Serruys PW, Foley DP, Jackson G, Bonnier H, Macaya C, Vrolix M, Branzi A, Shepherd J, Suryapranata H, de Feyter PJ, Melkert R, van Es GA, Pfister PJ. A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty. Eur Heart J. 1999; 20: 58-69.

[103] Herd JA, Ballantyne CM, Farmer JA, Ferguson JJ 3rd, Jones PH, West MS, Gould KL, Gotto AM Jr. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). Am J Cardiol. 1997; 80: 278-286.

[104] Riegger G, Abletshauser C, Ludwig M, Schwandt P, Widimsky J, Weidinger G, Welzel D. The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment. Atherosclerosis. 1999; 144: 263-270.

[105] Anderssen SA, Hjelstuen AK, Hjermann I, Bjerkan K, Holme I. Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives. Atherosclerosis. 2005; 178: 387-397.

[106] Bruckert E, Lievre M, Giral P, Crepaldi G, Masana L, Vrolix M, Leitersdorf E, Dejager S. Short-term efficacy and safety of extended- release fluvastatin in a large cohort of elderly patients. Am J Geriatr Cardiol. 2003; 12: 225-231.

[107] Ballantyne CM, Pazzucconi F, Pintó X, Reckless JP, Stein E, McKenney J, Bortolini M, Chiang YT. Efficacy and tolerability of fluvastatin extended-release delivery system: a pooled analysis. Clin Ther. 2001; 23: 177-192.

[108] Sonmez A, Baykal Y, Kilic M Yilmaz MI, Saglam K, Bulucu F, Kocar IH. Fluvastatin improves insulin resistance in nondiabetic dyslipidemic patients. Endocrine. 2003; 22: 151-153.

[109] Sonmez A, Dogru T, Tasci I Yilmaz MI, Pinar M, Naharci I, Bingol N, Kilic S, Demirtas A, Bingol S, Ozgurtas T, Erikci S. The effect of fluvastatin on plasma adiponectin levels in dyslipidaemia. Clin Endocrinol (Oxf). 2006; 64: 567-572.

[110] Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. New Engl J Med. 1995; 333: 1301-1308.

[111] Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med. 1998; 339: 1349-1357.

[112] Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Nakaya N, Nishimoto S, Muranaka M, Yamamoto A, Mizuno K, Ohashi Y; MEGA Study Group. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006; 368: 1155-1163.

[113] GISSI Prevenzione (GISSI-P) Investigators. Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). Ital Heart J. 2000; 1: 810-820.

[114] The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin vs Usual Care. JAMA. 2002; 288: 2998-3007.

[115] Keech A, Colquhoun D, Best J, Kirby A, Simes RJ, Hunt D, Hague W, Beller E, Arulchelvam M, Baker J, Tonkin A; LIPID Study Group . Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. Diabetes Care. 2003; 26: 2713-2721.

[116] Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. New Engl J Med. 1996; 335: 1001-1009.

[117] Zhou Z, Rahme E, Pilote L. Are statins created equal? Evidence from randomized trials of pravastatin, simvastatin, and atorvastatin or cardiovascular disease prevention. Am Heart J. 2006; 151: 273-281.

[118] Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care. 2009; 32: 1924-1929.

[119] Coleman CI, Reinhart.K., Kluger J, White CM. The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomized controlled trials. Curr Med Res Opin. 2008; 24: 1359-1362.

[120] Sukhija R, Prayaga S, Marashdeh M, Bursac Z, Kakar P, Bansal D, Sachdeva R, Kesan SH, Mehta JL. Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. J Investig Med. 2009; 57: 495-499.

[121] Baker WL, Talati R, White CM, Coleman CI. Differing effect of statins on insulin sensitivity in non-diabetics: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2010; 87: 98-107.

[122] Koh KK, Quon MJ, Han SH Lee Y, Kim SJ, Park JB, Shin EK. Differential metabolic effects of pravastatin and simvastatin in hypercholesterolemic patients. Atherosclerosis. 2009; 204: 483-490.

[123] Yee A, Majumdar SR, Simpson SH, McAlister FA, Tsuyukit RT, Johnson JA. Statin use in Type 2 diabetes mellitus is associated with a delay in starting insulin. Diabet Med. 2004; 21: 962-967.

[124] Yokote K, Saito Y; CHIBA. Influence of statins on glucose tolerance in patients with type 2 diabetes mellitus: subanalysis of the collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study). J Atheroscler Thromb. 2009; 16: 297-298.

[125] Lamendola C, Abbasi F, Chu JW Hutchinson H, Cain V, Leary E, McLaughlin T, Stein E, Reaven G. Comparative effects of rosuvastatin and gemfibrozil on glucose, insulin, and lipid metabolism in insulin-resistant, nondiabetic patients with combined dyslipidemia. Am J Cardiol. 2005; 95: 189-193.

[126] Yamakawa T, Takano T, Tanaka Si, Kadonosono K, Terauchi Y. Influence of pitavastatin on glucose tolerance in patients with type 2 diabetes mellitus. J Atheroscler Thromb. 2008;15: 269-275.

[127] Tajima N, Kurata H, Nakaya N et al. Pravastatin reduces the risk for cardiovascular disease in Japanese hypercholesterolemic patients with impaired fasting glucose or diabetes: Diabetes subanalysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study. Atherosclerosis. 2008; 199: 455-462.

[128] Preiss D, Seshasai SR, Welsh P et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011; 305: 2556-2564.

[129] Cannon CP, Braunwald E, McCabe CH et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004; 350: 1495-1504.

[130] LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005; 352: 1425-1435.

Annex 3

Summary Assessment Report of the PhVWP December 2011

Methotrexate – Risk of overdose due to erroneous daily intake of the weekly dose in rheumatologic and dermatologic indications

Key message

Product information for methotrexate for oral use in rheumatologic and dermatologic indications should emphasise that it should be taken once a week and patients should be informed of the risk of overdose due to erroneous daily intake of the intended weekly dose. Key elements for risk minimisation should be consistently reflected in product information across the EU to minimise the risk of inadvertent overdose.

Safety concern and reason for current safety review

Cases of overdose with methotrexate in rheumatologic and dermatologic indications were reported in the EU from January 2009 to August 2011 due to inadvertent daily instead of weekly intake, despite measures taken in most Member States to reduce this risk of error. In the reported cases, serious adverse reactions occurred, fatal in some cases, especially due to the haematological toxicity of methotrexate. The causes of errors in these cases range from prescribing and administration errors (mainly for hospitalised patients) to errors in self-administration (by patients at home, either inadvertently or by misunderstanding the medication schedule).

Given these cases, the PhVWP agreed to review how to further minimise the risk.

Clinical setting

Oral use of methotrexate is indicated, inter alia, in the treatment of active rheumatoid arthritis and psoriasis in adults. The therapeutic anti-inflammatory effects of methotrexate appear to be related at least in part to interruption of adenosine and possible effects on tumour necrosis factors (TNF) pathways. The immunosuppressive and toxic effects of methotrexate are due to the inhibition of an enzyme involved in the metabolism of folic acid, dihydrofolate reductase.

Information on the data assessed

The PhVWP assessed the case reports, further data from the marketing authorisation holders for methotrexate-containing products as well as information exchanged between Member States.

Outcome of the assessment

Following the assessment of the case reports and further data from the marketing authorisation holders for methotrexate-containing products, an exchange of information between Member States showed that these medication errors had been reported in several Member States where risk minimisation measures had already been taken, such as communication with healthcare professionals, the use of a supportive prescribing system or amendments to the product information. It also showed that information on this risk in the product information differed substantively between Member States and sometimes between products in the same Member State.

In the light of these results and supported by the conclusions of two publications [1-2], the PhVWP agreed on key elements of a simple message emphasising the need for adherence to once weekly intake and a consistent warning on the risks of overdose (in particular the risks of haematological and gastrointestinal reactions) for inclusion in the summaries of product characteristics and package leaflets of all methotrexate-containing products for oral use authorised in the EU for rheumatologic and dermatologic indications, together with the statement "take the prescribed dose once a week" for printing on the package (labelling), preferably on the vial's cap if possible. The PhVWP further agreed that the question of whether to maintain the option of dividing the weekly dose should be decided at national level, and that additional risk minimisation measures may likewise be implemented at national level if considered appropriate.

References

[1] Oral methotrexate: preventing avoidable overdose. Prescrire international. 2007; 16: 150-152.

[2] Blinova E, Volling J, Koczmara C, Greenall J. Oral methotrexate: preventing inadvertent daily administration. Can J Hosp Pharm. 2008; 61: 275-277.

Annex 4

Summary Assessment Report of the PhVWP December 2011

Montelukast – Risk of psychiatric adverse reactions in children

Key message

Psychiatric and behaviour-related adverse reactions have been reported in patients treated with montelukast. The current knowledge in this respect is adequately reflected in the existing EU product information and safety monitoring will continue through routine pharmacovigilance activities.

Safety concern and reason for current safety review

Following the assessment of the periodic safety update report (PSUR) for montelukast covering the period from 31 July 2006 to 30 July 2009, case reports, received through spontaneous reporting schemes, on suspected psychiatric and behaviour-related adverse reactions were further evaluated. Based on this evaluation, the originator marketing authorisation holder was requested to submit a risk management plan (RMP) focusing on the main and most severe psychiatric adverse reactions reported in children. The draft RMP was scheduled for review by the PhVWP.

Clinical setting

Montelukast is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene type-1 (CysLT1) receptor and is indicated for the treatment of asthma and allergic rhinitis.

Information on the data assessed

The data assessed included the originator marketing authorisation holder's draft RMP focusing on the main and most severe behaviour-related adverse reactions in children.

Outcome of the assessment

The PhVWP reviewed the RMP, and in particular whether the current risk management is sufficient or whether further pharmacovigilance activities or risk minimisation measures are warranted. The PhVWP concluded that the current EU product information is adequate in the light of the current knowledge and that the RMP should be finalised with the requirement to apply routine pharmacovigilance activities, including future PSURs, to closely monitor neuropsychiatric events and to give a summary evaluation in the next PSUR which is due later in 2012.

In this context, the PhVWP noted that a project focusing on suicidal adverse events associated with fluoxetine, risperidone and montelukast is being conducted by a group of experts in paediatric psychopharmacology within the framework of the European Child and Adolescent Paediatric Network (ECAPN), funded by the European Community's Seventh Framework Programme. The results of the project, which is anticipated to be completed in 2014, is expected to give further insight into the future evaluation of severe behavioural adverse events occurring in children treated with montelukast.

Annex 5

Summary Assessment Report of the PhVWP December 2011

Proton-pump inhibitors – Risk of hypomagnesaemia with long-term use

Key message

Proton-pump inhibitors (PPIs) may cause serious hypomagnesaemia and therefore for patients expected to be on prolonged treatment, especially when using other hypomagnesaemia-inducing medicines, healthcare professionals should consider measuring magnesium levels before and periodically during PPI treatment.

Safety concern and reason for current safety review

In March 2011, the Spanish competent authorities were made aware of a review by a regional pharmacovigilance centre in Spain investigating the risk of hypomagnesaemia in long-term users of proton-pump inhibitors (PPIs). The first case of hypomagnesaemia related to PPI intake was reported to that centre in 2008. An evaluation of all available data from spontaneous reporting in Spain, the published literature, the EudraVigilance database and other sources was performed in March 2011. A similar review had previously been carried out in the Netherlands, and additional information from the Dutch pharmacovigilance centre (Lareb) was also part of the Spanish assessment.

The PhVWP therefore agreed to conduct a review of this safety concern at EU level.

Clinical setting

A large number of medicinal products containing a proton-pump inhibitor (PPI) are authorised and constitute one of the most widely used classes of medicines in the EU. The PPIs included in this review were dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

The mechanism of PPI-induced hypomagnesaemia is unknown, and several hypotheses have been postulated. A relevant aspect of this adverse effect is that patients usually have symptoms after using PPIs for three months or longer. Hypomagnesaemia means low blood magnesium levels. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur.

Information on the data assessed

Case reports from spontaneous reporting schemes collected in the adverse reaction databases EudraVigilance and Vigibase (the database maintained by the Uppsala Monitoring Centre, the WHO Collaborating Centre for International Drug Monitoring) or reported in the medical literature [1-3] were assessed.

Outcome of the assessment

The PhVWP considered that the case reports showed that most of the patients presented several hypomagnesaemia symptoms and hospitalisation episodes in previous years, which may reflect the difficulties on recognising this adverse reaction.

The PhVWP concluded that the product information of all PPI-containing medicinal products authorised in the EU for long-term use should inform patients and healthcare professionals of the rare but potentially serious risk of hypomagnesaemia associated with PPI intake. Although this adverse reaction may be rare, the wide use of PPIs, the seriousness of a number of cases of hypomagnesaemia and the lack of awareness of healthcare professionals, which may delay diagnosis and treatment, support this conclusion.

The PhVWP therefore recommended that section 4.4 of the summaries of product characteristics on warnings and precautions for use should inform healthcare professionals that

- severe hypomagnesaemia has been reported in patients treated with PPIs for at least three months, and in most cases for a year;
- serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but may begin insidiously and be overlooked;
- in most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI; and that
- for patients expected to be on prolonged treatment, and particularly those who take PPIs with digoxin or other medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment;

and that section 4.8 on undesirable effects should inform healthcare professionals that hypomagnesaemia may occur as an adverse reaction with unknown frequency.

The package leaflets should be updated accordingly and additionally ask the patient to inform a healthcare professional promptly, should any symptom of hypomagnesaemia occur.

In addition, the PhVWP proposed communication on this safety concern to healthcare professionals at the level of Member States. It was noted that the issue is already in the public domain after the publication of a number of case reports and recent public statements from several authorities.

References

[1] Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Engl J Med. 2006; 355: 1834-1836.

[2] Cundy T, McKay JD. Proton pump inhibitors and severe hypomagnesaemia. J Current Opinion in Gastroenterology. 2011; 27: 180-185.

[3] Swaminathan K, Wilson J. Elusive cause of hypomagnesaemia. Br Med J. 2011; 343: d5087.