平成１８年１１月１０日（金）
医薬食品局安全対策課
課長　伏見　環（内線2747）
課長補佐　丈達　泰史（内線2748）

「新型インフルエンザに関するＱ＆Ａ」の一部改訂について

「新型インフルエンザに関するＱ＆Ａ」中の「Ⅳ．リン酸オセルタミビル（商品名：タミフル）について」を一部改訂しましたので、お知らせします。

（別添）
新型インフルエンザに関するQ&A（平成１８年１１月１０日改訂）より該当部分を抜粋

（別添）

新型インフルエンザに関するＱ＆Ａ（抜粋）

平成１７年１１月１５日
（同年１１月３０日改訂）
（同年１２月１５日改訂）
（平成１８年１月２７日改訂）
（同年７月１０日改訂）
（同年１１月１日改訂）
（同年１１月１０日改訂）

Ⅳ-6　タミフルを服用した後の異常行動等による小児の死亡例が報道されていますが、厚生労働省としては、タミフルの安全性についてどのように考えているのですか。

Answer

タミフルを服用した１６歳以下の異常行動によるものを含む小児１６例（治験時１例を含む。平成１８年１０月３１日現在。）の死亡が報告されています。

小児の死亡事例とタミフルとの関係については、平成１７年１１月１８日に米国食品医薬品局（ＦＤＡ）が評価を依頼した小児諮問委員会においても、「現時点で得られている事実からは、因果関係を示す証拠はないと考えられる」と評価されています。

また、日本小児科学会も、「現時点でタミフルとこれらの死亡についての因果関係が明らかなものはなかった。」との見解を平成１７年１１月３０日に公表しています。

厚生労働省としては、平成１８年１月２７日に薬事・食品衛生審議会医薬品等安全対策部会安全対策調査会を開催し、また、その後も、専門家の意見を随時聞いたところ、タミフルと死亡との関係については否定的であることなどから、現段階でタミフルの安全性に重大な懸念があるとは考えていません。

医師の指示に従って適切に服用するとともに、副作用の症状があらわれたときは、医師、薬剤師に相談して下さい。

なお、平成１７年度厚生労働科学研究「インフルエンザに伴う随伴症状の発現状況に関する調査研究」の報告書※によると、約２，８００名の小児等を対象に、異常言動の発現について、タミフル未使用群とタミフル使用群を比較したところ、統計学的に有意な差は見られなかったと報告されています。

※　医薬品・医療機器等安全性情報No.229（http://www.mhlw.go.jp/houdou/2006/10/h1026-1.html）の参考資料を御参照下さい。

Ⅳ-7　タミフルを服用した後の成人の死亡例も報告されているようですが、厚生労働省としては、タミフルの安全性についてどのように考えているのですか。

Answer

タミフルを服用した成人（１７歳以上）の死亡が報告されていますが、平成１８年１月２７日に薬事・食品衛生審議会医薬品等安全対策部会安全対策調査会を開催し、また、その後も、専門家の意見を随時聞いたところ、中毒性表皮壊死症（Lyell症候群）※1、腎障害、肝障害及びアナフィラキシーショックによる死亡５例については因果関係を否定できないものの、それ以外の３３例（平成１８年１０月３１日現在）についてはタミフルと死亡との因果関係は否定的であるとされています※2。

タミフルの服用に伴う中毒性表皮壊死症、肝障害及びアナフィラキシーショックについては平成１４年１０月に、腎障害については平成１５年７月に、添付文書の使用上の注意に記載し、ごくまれにあらわれる旨注意を喚起しているところです。

したがって、厚生労働省としては、現段階でタミフルの安全性に重大な懸念があるとは考えていません。

医師の指示に従って適切に服用するとともに、副作用の症状があらわれたときは、医師、薬剤師に相談して下さい。

※１　中毒性表皮壊死症は、一般用医薬品を含めた多くの医薬品においてごくまれにあらわれる副作用として報告されています。医薬品・医療機器等安全性情報No.218（http://www.mhlw.go.jp/houdou/2005/10/h1027-1.html）の「２．医薬品による重篤な皮膚障害について」を御参照下さい。

※２　タミフル発売（平成１３年２月）後に厚生労働省に報告された事例については上記のとおりですが、これとは別に、タミフルの製造販売業者は、そもそもタミフルとの因果関係がないものとして死亡１６例を把握していると聞いています（平成１８年１０月３１日現在）。

（参考：タミフルの有用性について）

（１）医薬品は、人体にとって本来異物であり、何らかの副作用が生ずることは避け難いものです。このため、治療上の効能・効果と副作用の両者を考慮した上で、医薬品の有用性が評価されるものです。

（２）タミフルについては、

○　ＷＨＯや欧米においても、インフルエンザに有効な医薬品は実質的にタミフルしかなく、新型インフルエンザ対策の重要な柱として位置付けられており、

○　タミフルとの因果関係を否定できない死亡例が上記のとおり報告されていますが、ごく限られたものです。

（３）したがって、タミフルは医薬品として高い有用性が認められるものであり、通常のインフルエンザ及び新型インフルエンザ対策の上で、必須の医薬品と考えられています。

米国におけるリン酸オセルタミビルの添付文書の改訂について

「使用上の注意」の項目に「精神神経症状」を新たに設置して、次の文章を記載

（平成18年11月13日）

Neuropsychiatric Events

There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period.

（仮訳）

精神神経症状

インフルエンザ患者においてタミフル服用後に発現した自傷行為や譫妄について、市販後の報告（多くは日本）がなされています。報告は主に小児患者のものです。タミフルのこれら事象に対する相対的な寄与は不明です。インフルエンザ患者は、治療期間中は、異常行動の兆候について厳重に観察されなければなりません。

Roche

Pharmaceuticals

November 13, 2006

IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

Roche Laboratories Inc. would like to advise you of a recent update to the TAMIFLU® (oseltamivir phosphate) package insert. The revision to the product label is a result of information about adverse events reported during postmarketing clinical use of TAMIFLU.

The revised PRECAUTIONS section of the TAMIFLU Capsules and Oral Suspension package insert now includes the following information and guidance under a new Neuropsychiatric Events subheading:

> ***Neuropsychiatric Events***
>
> There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period.

In addition, the following statement has been added to the TAMIFLU Patient Information, in the ***What are the possible side effects of TAMIFLU?*** section:

> People with the flu, particularly children, may be at an increased risk of self-injury and confusion shortly after taking TAMIFLU and should be closely monitored for signs of unusual behavior. A healthcare professional should be contacted immediately if the patient taking TAMIFLU shows any signs of unusual behavior.

TAMIFLU is indicated for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days. TAMIFLU is indicated for the prophylaxis of influenza in patients 1 year and older. TAMIFLU is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee. Please see page 2 of this letter for other important TAMIFLU safety information.

We encourage you to become familiar with these label revisions. If you have any questions or require additional information concerning TAMIFLU, please contact the Roche Pharmaceuticals Service Center at 1-800-526-6367. An updated package insert is enclosed for your information. In addition, healthcare professionals can access the revised TAMIFLU complete product information at http://www.rocheusa.com/products/tamiflu/pi.pdf.

Roche Laboratories will continue to monitor the safety of TAMIFLU through established reporting mechanisms and notify regulatory authorities of any serious adverse events for evaluation. We will continue to provide you with the most current product information for TAMIFLU moving forward. You can assist us in monitoring the safety of TAMIFLU by reporting adverse reactions to us at 1-800-526-6367, by FAX at 1-800-532-3931, or to FDA at www.fda.gov/medwatch, or by mail to MedWatch, HF-2, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20851.

Roche Laboratories Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Roche

Safety Information

There is no evidence for efficacy against any illness caused by agents other than influenza types A and B.

Treatment efficacy in subjects with chronic cardiac and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population.

No information is available regarding treatment of influenza in patients at imminent risk of requiring hospitalization.

Efficacy of Tamiflu has not been established in immunocompromised patients.

Safety and efficacy of repeated treatment of prophylaxis courses have not been studied.

There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period.

In postmarketing experience, rare cases of anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme, have been reported with TAMIFLU.

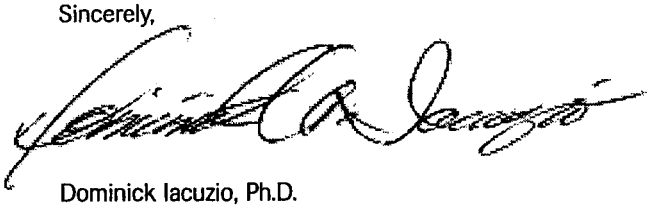
In treatment studies in adult patients, the most frequently reported adverse events (incidence ≥ 1%) were nausea and vomiting. Other events reported numerically more frequently in patients taking TAMIFLU compared with placebo were bronchitis, insomnia and vertigo. In treatment studies in patients 1 to 12 years old, the most frequently reported adverse event (incidence ≥ 1%) was vomiting (15%). Other events reported more frequently in patients taking TAMIFLU compared with placebo included abdominal pain (5% vs 4%), epistaxis (3% vs 3%), ear disorder (2% vs 1%) and conjunctivitis (1% vs ≤ 1%).

In prophylaxis studies in adult patients, adverse events were similar to those seen in the treatment studies. Events reported more frequently in patients taking TAMIFLU compared with placebo (incidence ≥ 1%) were nausea (7% vs 3%), vomiting (2% vs 1%), diarrhea (3% vs 2%), abdominal pain (2% vs 1%), dizziness (1% vs 1%), headache (18% vs 18%) and insomnia (1% vs 1%). In household prophylaxis trial that included patients 1 to 12 years old, adverse events were consistent with those observed in pediatric treatment studies, with GI events being the most frequently observed.

The concurrent use of TAMIFLU with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of the potential for interference between these products, LAIV should not be administered within 2 weeks before or 48 hours after administration of TAMIFLU, unless medically indicated. The concern about possible interference arises from the potential for antiviral drugs to inhibit replication of live vaccine virus. Trivalent inactivated influenza vaccine can be administered at any time relative to use of TAMIFLU.

Vaccination is considered the first line of defense against influenza.

Sincerely,



Dominick Iacuzio, Ph.D.

Medical Director, Roche Laboratories Inc.

Enclosures:

- Complete Product Information for TAMIFLU® (oseltamivir phosphate) Capsules and for Oral Suspension.
- TAMIFLU® (oseltamivir phosphate) Patient Information

（仮訳）

ロンドン、11 月 17 日
Doc. Ref. :EMEA/460883/2006

プレスリリース
薬事審査委員会（CHMP）からの会合ハイライト（抜粋）
2006 年 11 月 13 日～16 日

タミフルに関する更新情報

最近のメディアの関心を踏まえて、薬事審査委員会（CHMP）は、タミフル服用中の精神神経障害に関する新規の安全性シグナルはなく、よって現行のEUにおける医師への処方情報を変更する必要はないという2005年12月15日の見解を再確認した。

当局は、タミフルの承認以降、タミフルの使用に関連する精神神経障害の兆候に注目してきたが、タミフルの使用とこれらの兆候に因果関係は確認されなかった。当局はロシュ社に、2003年2月の欧州におけるタミフルの上市以降のそのような行動に関する全ての報告を厳重に追跡するよう要求していたところである。

ロシュ社が供給するタミフルは、2002年6月にEUで承認され、現在の適応は、成人および1歳以上の小児におけるインフルエンザの予防及び治療とされている。

以上

European Medicines Agency
Press office

London, 17 November 2006
Doc. Ref. EMEA/460883/2006

PRESS RELEASE
Meeting highlights from the Committee for Medicinal Products for Human Use, 13-16 November 2006

Initial marketing authorisation applications

The Committee for Medicinal Products for Human Use (CHMP) gave positive opinions on initial marketing authorisation applications, including one opinion for a medicinal product that is intended for the treatment of patients suffering from rare diseases:

- **Exforge, Dafiro, Copalia** and **Imprida** (amlodipin besylate/valsartan), from Novartis Europharm Ltd, are intended for the treatment of essential hypertension. EMEA review time for Exforge was 173 days and 80 days for Dafiro, Copalia and Imprida.
- **Inovelon** (rufinamide), from Eisai Ltd, is intended for the treatment of seizures associated with Lennox-Gastaut syndrome, one of the most severe forms of childhood epilepsy. EMEA review time was 208 days. Inovelon is the **34th orphan medicinal product** to receive a positive CHMP opinion.
- **Lucentis** (ranibizumab), from Novartis Europharm Ltd, for the treatment of neovascular (wet) age-related macular degeneration (AMD), which causes damage to the retina by abnormal blood vessels growing and leaking into the eye. EMEA review time was 195 days.

The Committee adopted a negative opinion for **Mycograb** (efungumab), from NeuTec Pharma Plc. Mycograb, an orphan medicinal product, was intended to be used for the treatment of invasive candidiasis, in combination with amphotericin B (including lipid-associated formulations). EMEA review time was 207 days.

A separate question and answer document explaining the grounds for the negative opinion can be found here.

Extensions of indication

The Committee gave positive opinions for applications for extensions of indication, adding new treatment options for the following previously approved medicines:

- **Keppra** (levetiracetam), from UCB S.A., to include the treatment of primary generalised tonic-clonic seizures as adjunctive therapy in adults and adolescents from 12 years of age with idiopathic generalised epilepsy. Keppra was first granted a marketing authorisation in the European Union on 29 September 2000 and is currently indicated to treat partial onset seizures and myoclonic seizures in patients with epilepsy.
- **Neupro** (rotigotine), from Schwarz BioSciences GmbH, to include the treatment of the signs and symptoms of advanced-stage idiopathic Parkinson's disease in combination with levodopa. Neupro was first granted a marketing authorisation in the European Union on 15 February 2006 and is currently indicated to treat signs and symptoms of early stage idiopathic Parkinson's disease.

'Informed consent' applications

The Agency adopted positive opinions for a number of medicinal products for which 'informed consent' applications were submitted. This type of application requires that reference is made to an authorised medicinal product and that the marketing authorisation holder of this reference product has given consent to the use of the dossier in the application procedure.

- **Insulin Human Winthrop** (insulin human), from Sanofi-Aventis Deutschland GmbH, is recommended for the treatment of diabetes mellitus where treatment with insulin is required. The

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E-mail: mail@emea.europa.eu http://www.emea.europa.eu

reference product for this application is Insuman, also from Sanofi-Aventis Deutschland GmbH. EMEA review time was 110 days.

- **Irbesartan Hydrochlorothiazide BMS** (irbesartan/hydrochloride), from Bristol-Myers Squibb Pharma EEIG, is intended for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on Irbesartan or Hydrochlorothiazide alone. The reference product for this application is Karvezide, also from Bristol-Myers Squibb Pharma EEIG. EMEA review time was 50 days.
- **Irbesartan Hydrochlorothiazide Winthrop** (irbesartan/hydrochloride), from Sanofi Pharma Bristol-Myers Squibb SNC, is recommended for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on Irbesartan or Hydrochlorothiazide alone. The reference product for this application is CoAprovel, also from Sanofi Pharma Bristol-Myers Squibb SNC. EMEA review time was 50 days.
- **Irbesartan BMS** (irbesartan), from Bristol-Myers Squibb Pharma EEIG, is recommended for treatment of essential hypertension and treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an anti-hypertensive regimen. The reference product for this application is Karvea, also from Bristol-Myers Squibb Pharma EEIG. EMEA review time was 50 days.
- **Irbesartan Winthrop** (irbesartan), from Sanofi Pharma Bristol-Myers Squibb SNC, is recommended for the treatment of essential hypertension and treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an anti-hypertensive regimen. The reference product for this application is Aprovel, also from Sanofi Pharma Bristol-Myers Squibb SNC. EMEA review time was 50 days.

New contraindications

The Committee recommended to add a contraindication for **Ketek and Levviax** (telithromycin), from Aventis Pharma S.A., saying that Ketek or Levviax must not be used in patients with previous history of hepatitis and/or jaundice associated with the use of telithromycin. Ketek and Levviax were first granted marketing authorisation on 9 July 2001 and are currently authorised for a number of respiratory-tract infections.

Summaries of opinions, including more detailed information on the new indications or contraindications for all products mentioned above are available and can be found here.

Referral procedures concluded

The Committee concluded two referral procedures, one for **Ciprofloxacin Nycomed** 2mg/ml solution for infusion (ciprofloxacin), from Nycomed Danmark APS, and one for **Ciprofloxacine Kabi** (ciprofloxacin hydrogen sulphate), from Fresenius Kabi Nederland B.V. The Committee recommended the harmonisation of the dosing recommendation for the treatment of complicated urinary tract infections, and of the maximum daily dose for adults in approved indications, across the European Union. The procedures were initiated under Article 29 of Directive 2001/83/EC as amended because of disagreement in the context of the mutual recognition procedure.

Re-examination application withdrawn

The Committee was informed by Les Laboratoires Servier of their decision to withdraw the application for re-examination of the negative opinion for **Valdoxan** and **Thymanax** (agomelatine), adopted by the Committee on 27 July 2006.

A question and answer document explaining the grounds for the negative opinion and the next steps in the procedure can be found here.

Update on Tamiflu

Following recent media interest, the CHMP reaffirmed its position of 15 December 2005 that there is no new safety signal relating to psychiatric disorders while taking Tamiflu and therefore no need to change the current prescribing advice to doctors in the EU.

The Agency has been aware of incidents of psychiatric disorders associated with the use of Tamiflu since its approval. No causal relationship has been identified between use of Tamiflu and these incidents. The Agency has required Roche to follow closely all reports of such behaviour since the launch of Tamiflu in Europe in February 2003.

Tamiflu, from Roche, was approved in the European Union in June 2002 and is currently indicated for prevention and treatment of influenza in adults and children aged one year or above.

A more detailed CHMP meeting report will be published shortly.

--ENDS--

Media enquiries only to:
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