Safeguarding public health

UK Suspected Adverse Drug Reaction (ADR) Analysis

Influenza antivirals - oseltamivir (Tamiflu) and zanamivir (Relenza)

12 November 2009

This report summarises all UK reports of suspected adverse drug reactions (ADRs)/side effects to influenza antiviral medicines Tamiflu (oseltamivir) and Relenza (zanamivir) received by MHRA between Wednesday 1st April 2009 and Thursday 5th November 2009 (inclusive)[1]. These reports have been voluntarily submitted to MHRA by healthcare professionals and members of the public via the MHRA's 'Swine Flu ADR Portal' (www.mhra.gov.uk/swineflu) and the Yellow Card Scheme. It also includes all UK reports submitted by the Marketing Authorisation holders for Tamiflu and Relenza as part of their legal requirements. The suspected ADRs listed in the attached Drug Analysis Prints have been coded using 'MedDRA' terminology[2].

It is important to note that a report of a reaction does not necessarily mean that it has been caused by the drug in question. We encourage reporters to report *suspected* ADRs i.e. the reporter does not have to be sure of a causal association between the drug and the reaction – a mere suspicion will suffice. Therefore, reports submitted to MHRA may be true adverse effects of the drug or they may be coincidental events (e.g. due to underlying medical conditions) that would have occurred anyway in the absence of exposure to the drug in question. For this reason **this summary is not a list of known or proven adverse reactions to Tamiflu or Relenza and must not be interpreted and used as such**. A list of the recognised adverse effects is provided in the product information for Tamiflu and Relenza. The product information for Tamiflu has recently been updated; please visit our website for the latest copy (www.mhra.gov.uk/swineflu).

Reporting rates are highly variable and are dependent on many factors. Therefore these data cannot be used to determine the frequency of occurrence of ADRs to Tamiflu and Relenza. Furthermore, the fact that these two drugs are likely to be used in different patient populations during the current swine flu A/H1N1 pandemic, **a direct comparison of the relative safety of Tamiflu and Relenza can not be made using these data**.

All reports of suspected ADRs to Tamiflu and Relenza continue to be closely monitored by a dedicated team of drug safety specialists at the MHRA.

Headline summary:

- A total of 850,600 treatment courses of Tamiflu and 11,485 treatment courses of Relenza have been collected via the National Pandemic Flu Service in England between 23rd July 2009 and 3rd November 2009 (inclusive)[3]. These data do not include courses of oseltamivir and zanamivir prescribed or obtained outside of the NPFS system (e.g. GP voucher; hospital use), or courses of oseltamivir and zanamivir used in Scotland, Wales or Northern Ireland.

- Up to, and including Thursday 5th November 2009, the MHRA has received a total of 909 reports of suspected ADRs for Tamiflu and 19[4] reports for Relenza.

[1] Suspected ADR data are released with a 1 week delay in order to ensure that MHRA has time to validate, extract and assess the data before publication.
[2] MedDRA - the Medical Dictionary for Regulatory Activities - is a standardised, medically validated adverse event terminology system used within the international medicines regulatory environment.
[3] Data obtained from, and used with permission from the Department of Health, England.
[4] A previously reported zanamivir case has been removed as it was reported from outside of the UK.

Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

- The most frequently reported suspected ADRs are consistent with the signs and symptoms of recognised adverse effects of the antivirals or of flu-like illness.

- No new safety concerns have been identified for either drug and no changes to the product safety information are required. Patients should continue to take Tamiflu or Relenza as advised by their healthcare provider.

- The balance of risks and benefits for Tamiflu and Relenza within their licensed indications remains positive.

- For Tamiflu, we continue to closely monitor a number of recognised adverse effects. We also continue to closely monitor reports suggestive of a possible interaction between Tamiflu and warfarin resulting in an increased risk of bleeding. However, there is currently no strong evidence of an interaction between the two drugs (see below).

- When identified, information on new and emerging safety signals will be provided in this report together with details of any resulting regulatory action or changes to prescribing advice deemed necessary.

SUSPECTED ADR REPORTS RECEIVED FOR TAMIFLU

A total of 909 reports (including 1612 suspected adverse reactions[5]) have been reported for Tamiflu in the UK since 1st April 2009.

The most commonly reported suspected ADRs are consistent with the signs and symptoms of recognised side effects of Tamiflu such as mild allergic reactions as well as gastrointestinal events, headache and dizziness which can also be caused by flu-like illness.

No new safety issues have been identified.

Adverse events under close monitoring by MHRA

Possible Drug Interaction between Tamiflu and Warfarin

We continue to keep under review reports suggestive of a possible drug interaction between Tamiflu and warfarin (a drug used to prevent blood clotting) resulting in prolonged blood clotting time. Blood clotting control can be affected by flu and associated symptoms (e.g. decreased appetite and anorexia). Therefore it is very difficult to establish whether these cases represent a true drug interaction between Tamiflu and warfarin or whether blood clotting control in these patients may have been affected by underlying infection and associated symptoms.
Other data from clinical trials conducted by the Marketing Authorisation holder do not support the existence of an interaction between Tamiflu and warfarin.

Currently there is no strong evidence of an interaction between the two drugs. Patients should continue to take Tamiflu and warfarin as advised by their healthcare provider.

All reports of a possible interaction with warfarin remain under close review by the MHRA.

Suspected ADRs with a fatal outcome

We have received eight reports in which the patient died following treatment with Tamiflu; two cases of unexplained death and single cases of cardiac arrest; acute hepatic failure; pancreatitis; perforated duodenal ulcer; intracerebral haemorrhage and vomiting in a patient who was also receiving chemotherapy. These cases have been fully evaluated and

[5] A single report may contain more than one suspected adverse reaction

in none of these is there evidence to confirm that Tamiflu was directly responsible for the fatal event. Underlying medical conditions and/or concurrent infection provide a more plausible alternative explanation for the events.

Neuropsychiatric adverse reactions
Neuropsychiatric adverse reactions, including convulsions and delirium (with symptoms such as confusion, abnormal behaviour, hallucinations, agitation, anxiety and nightmares) are listed as possible side effects in the Tamiflu product information.

However, influenza infection itself can be associated with a variety of neurologic and behavioural symptoms including the above, sometimes without obvious signs of a severe infection. Some studies have found that these types of event are no more frequent in influenza patients who have taken Tamiflu when compared to those who have not taken the drug. It therefore remains unclear whether these neuropsychiatric events may be a true side effect of Tamiflu or whether they are due to underlying infection (or a combination of both).

Reported cases of neuropsychiatric adverse effects will remain under close review by MHRA but those reported so far do not raise any new safety concerns. Nonetheless, patients should remain vigilant to the possibility of such events and discuss any serious concerns with their healthcare provider.

Serious skin reactions
Serious skin reactions including Erythema multiforme (EM), Stevens Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) are listed in the side effects section of the product information for Tamiflu. A number of such reactions have been reported for Tamiflu in the UK since 1st April but available epidemiological data suggest that these types of skin reactions can be caused by a number of different types of insults including viral infections. It therefore remains unclear whether reported cases of severe skin disorders are due to exposure to Tamiflu or to the underlying infection and associated illness.

The MHRA continues to keep such reports under close review.

Liver reactions
A Europe-wide review of Liver reactions reported for Tamiflu has previously been conducted; a causal association with Tamiflu could not be established. However as a precautionary measure, serious adverse effects on the liver including fulminant hepatic failure were added to side-effects section of the EU product information for Tamiflu as a result of isolated cases reported outside of the EU. MHRA has received a number of reports of suspected liver reactions to Tamiflu since April 2009; in some of the reports of abnormal liver function a causal association with Tamiflu can not be excluded. However, for the more serious liver events including the three cases of liver failure, there are more likely alternative causes. Nevertheless, we continue to closely monitor all suspected liver reactions to Tamiflu.

Safety in pregnancy
One case of spontaneous abortion occurring in the first trimester of pregnancy and one case of anencephaly (a neural tube defect) have been reported for Tamiflu in the UK. Both cases contain limited information. Spontaneous abortion is not uncommon in early pregnancy – the available epidemiological data suggest that one in four women who become pregnant will suffer a spontaneous abortion and that the risk is greatest during the first trimester. Inevitably therefore, spontaneous abortion may occur coincidentally following exposure to Tamiflu without the drug

playing any causal role in the event. Other factors such as obstetric history, underlying medical conditions, and exposure to chemicals, smoking status and alcohol use can all influence the risk of spontaneous abortion.

Currently there is no evidence to suggest that Tamiflu carries any risks (maternal, foetal, perinatal or postnatal) when used during pregnancy. A recent review of available evidence by European regulatory authorities led to a recommendation that, due to the potentially serious risks of H1N1 swine influenza in pregnancy, the benefits of using Tamiflu in treating influenza in pregnant or breastfeeding women outweigh any known risks.

SUSPECTED ADR REPORTS RECEIVED FOR RELENZA (zanamivir)

A total of 19[6] reports (including 37 suspected adverse reactions[3]) have been reported for Relenza in the UK since 1st April 2009. In one of these reports the suspected adverse reaction was fatal.

Most of the reported suspected ADRs are consistent with the signs and symptoms of known side effects of Relenza such as allergic reactions and bronchospasm. Most other reported events such as diarrhoea, nausea, vomiting, fatigue, headache and dizziness can be caused by flu-like illness.

No new safety issues have been identified.

Suspected ADRs with a fatal outcome

One suspected ADR with a fatal outcome has been reported for Relenza to date. This is a case of intra-uterine death which occurred during the third trimester of pregnancy. We have very limited information regarding this case, preventing full causality assessment. Further information has been requested. Currently there is no evidence to suggest that Relenza carries any risks (either to the mother or to the baby) when used during pregnancy (see safety in pregnancy below).

Safety in pregnancy

One case of spontaneous abortion occurring in the first trimester of pregnancy has been reported for Relenza. The report contains limited information which prevents full causality assessment; further information has been requested. Spontaneous abortion is not uncommon in early pregnancy – the available epidemiological data suggest that one in four women who become pregnant will suffer a spontaneous abortion and that the risk is greatest during the first trimester. Inevitably therefore spontaneous abortion may occur coincidentally following exposure to Relenza without the drug playing any causal role in the event. Other factors such as obstetric history, underlying medical conditions, and exposure to chemicals, smoking status and alcohol use can all influence the risk of spontaneous abortion.

Currently there is no evidence to suggest that Relenza carries any risks (either to the mother or to the baby) when used during pregnancy. A recent review of available evidence by European regulatory authorities led to a recommendation that, due to the potentially serious risks of H1N1 swine influenza in pregnancy, the benefits of using Relenza (and Tamiflu) in treating influenza in pregnant or breastfeeding women outweigh any known risks.

[6] A previously reported zanamivir case has been removed as it was reported from outside of the UK.

Drug Analysis Print
Drug Name: Tamiflu

Run Date: 1 April 2009 to 5 November 2009		
Total number of reactions: 1612	**Total number of ADR reports:** 909	**Total number of fatal ADR reports:** 8

System Organ Class	Reactions	Fatal Reactions
Blood and lymphatic system disorders	9	0
Cardiac disorders	22	1
Congenital, familial and genetic disorders	1	0
Ear and labyrinth disorders	11	0
Endocrine disorders	1	0
Eye disorders	34	0
Gastrointestinal disorders	527	3
General disorders and administration site conditions	94	2
Hepatobiliary disorders	21	1
Immune system disorders	10	0
Infections and infestations	21	0
Injury, poisoning and procedural complications	9	0
Investigations	50	0
Metabolism and nutrition disorders	12	0
Musculoskeletal and connective tissue disorders	30	0
Nervous system disorders	158	1
Pregnancy, puerperium and perinatal conditions	1	0
Psychiatric disorders	212	0
Renal and urinary disorders	13	0
Reproductive system and breast disorders	9	0
Respiratory, thoracic and mediastinal disorders	38	0
Skin and subcutaneous tissue disorders	319	0
Vascular disorders	10	0
Total	1612	8

Glossary/Abbreviations

ADR - Adverse Drug Reaction

Age group - lists which age groups are included in the Drug Analysis Print - either ALL, Adolescent, Adult, Child, Elderly, Infant or Neonate

Data lock date - shows data on the database at this specified date and time

HLT - High Level Term - see definition of MedDRA

MEDRA - this stands for Medical Dictionary for Regulatory Activities, which is the internationally agreed list of terms used for Medicines Regulation. MedDRA groups related adverse drug reaction terms in a hierarchical structure whereby the 'preferred term' (PT) (e.g. tunnel vision) is grouped under the broader heading the 'high level term' (HLT) (e.g. visual field disorders). 'High level terms' are contained within the 'system organ class' (SOC) (e.g. eye disorders). The 'preferred term' is the most specific term on the Drug Analysis Print, while the 'system organ class' is the most general

Multi active constituent products - contain the drug constituent of interest plus one or more other drug constituents (e.g. co-codamol contains paracetamol and codeine)

NEC - appears in MedDRA and stands for Not Elsewhere Classified

NOS - appears in MedDRA and stands for Not Otherwise Specified

PBG - Product Brand Generic - this means drug brand name e.g. Amoxil is a PBG for the drug substance amoxic

Products included in this print - this is a list of the products for which at least one suspected Adverse Drug Reaction (ADR) report has been received that specifies that product as a 'suspected drug' (i.e. suspected causal association with the reaction). It does not provide an exhaustive list of the products which contain the named drug substance

PT - Preferred Term - see definition of MedDRA

Reaction - defines which ADRs are included in the Drug Analysis Print - either ALL, Serious or Non-Serious

Reporter type - lists the reporter types which are included in the Drug Analysis Print - either Patient, Health Professional or ALL (i.e. both)

Report run date - the date the Drug Analysis Print was produced

Route of admin - lists the route of administration of the suspect drug for which reports are included in the Drug Analysis Print, e.g. ORAL only includes reports where the suspect drug was specified as having been taken by the oral route, or ALL which includes all routes of administration

Spontaneous - suspected ADR reports sent in to the Yellow Card Scheme are called spontaneous reports

Single active constituent products - contain only the drug substance of interest

System Organ Class (SOC) - this is the highest level in MedDRA which groups together reactions that affect similar systems/organs in the body

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Blood and lymphatic system disorders		
Anaemias haemolytic immune		
Anaemia haemolytic autoimmune	1	0
Haemolyses NEC		
Haemolysis	1	0
Leukocytoses NEC		
Neutrophilia	1	0
Lymphatic system disorders NEC		
Lymphadenopathy	1	0
Neutropenias		
Red blood cell abnormal findings NEC		
Macrocytosis	1	0
Thrombocytopenias		
Thrombocytopenia	3	0
Coagulopathies		
Abnormal clotting factor	1	0
Blood and lymphatic system disorders SOC Total	9	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Cardiac disorders		
Cardiac signs and symptoms NEC		
Cyanosis	1	0
Palpitations	10	0
Cardiomyopathies		
Congestive cardiomyopathy	1	0
Noninfectious myocarditis		
Myocarditis	1	0
Rate and rhythm disorders NEC		
Arrhythmia	1	0
Bradycardia	1	0
Tachycardia	1	0
Supraventricular arrhythmias		
Atrial fibrillation	2	0
Sinus arrhythmia	1	0
Sinus bradycardia	1	0
Ventricular arrhythmias and cardiac arrest		
Cardiac arrest	1	1
Ventricular arrhythmia	1	0
Cardiac disorders SOC Total	22	1

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Congenital, familial and genetic disorders		
Cerebral disorders congenital		
Anencephaly	1	0
Congenital, familial and genetic disorders SOC Total	1	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Ear and labyrinth disorders		
Inner ear signs and symptoms		
Tinnitus	4	0
Vertigo	5	0
Inner ear disorders NEC		
Meniere's disease	1	0
Ear disorders NEC		
Ear pain	1	0
Ear and labyrinth disorders SOC Total	11	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Endocrine disorders		
Thyroid hyperfunction disorders		
Hyperthyroidism	1	0
Endocrine disorders SOC Total	1	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Eye disorders		
Blindness (excl colour blindness)		
Blindness transient	1	0
Conjunctival infections, irritations and inflammations		
Conjunctivitis	3	0
Conjunctival and corneal bleeding and vascular disorders		
Conjunctival haemorrhage	1	0
Lacrimal disorders		
Lacrimation increased	1	0
Lid, lash and lacrimal infections, irritations and inflammations		
Blepharitis	2	0
Eyelid oedema	2	0
Ocular bleeding and vascular disorders NEC		
Eye haemorrhage	1	0
Ocular disorders NEC		
Eye pain	1	0
Eye swelling	4	0
Ocular icterus	1	0
Eyelid disorder	2	0
Ocular infections, inflammations and associated manifestations		
Eye pruritus	2	0
Ocular nerve and muscle disorders		
Strabismus	1	0
Ocular sensation disorders		
Abnormal sensation in eye	1	0
Photophobia	4	0
Visual disorders NEC		
Diplopia	1	0
Vision blurred	2	0
Visual impairment	4	0
Eye disorders SOC Total	34	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Gastrointestinal disorders		
Colitis (excl infective)		
Neutropenic colitis	1	0
Diarrhoea (excl infective)		
Diarrhoea	60	0
Diarrhoea haemorrhagic	4	0
Duodenal ulcers and perforation		
Duodenal ulcer	1	1
Dyspeptic signs and symptoms		
Dyspepsia	7	0
Flatulence, bloating and distension		
Abdominal distension	3	0
Flatulence	1	0
Gastritis (excl infective)		
Gastritis	1	0
Gastrointestinal and abdominal pains (excl oral and throat)		
Abdominal pain	34	0
Abdominal pain upper	33	0
Gastrointestinal pain	1	0
Gastrointestinal atonic and hypomotility disorders NEC		
Constipation	1	0
Non-site specific gastrointestinal haemorrhages		
Haematemesis	7	0
Lower gastrointestinal haemorrhage	1	0
Gingival disorders NEC		
Gingival disorder	1	0
Gingivitis	2	0
Gingival pains		
Gingival pain	1	0
Intestinal haemorrhages		
Rectal haemorrhage	5	0
Gastrointestinal signs and symptoms NEC		
Abdominal discomfort	1	0
Dysphagia	1	0

Stomach discomfort	2	0
Nausea and vomiting symptoms		
Nausea	82	0
Retching	3	0
Vomiting	201	1
Vomiting projectile	3	0
Regurgitation	1	0
Oral dryness and saliva altered		
Dry mouth	1	0
Oral soft tissue disorders NEC		
Cheilitis	3	0
Lip swelling	11	0
Lip ulceration	1	0
Chapped lips	1	0
Oral soft tissue pain and paraesthesia		
Oral pain	2	0
Paraesthesia oral	3	0
Oral soft tissue swelling and oedema		
Gingival swelling	1	0
Oedema mouth	2	0
Oral soft tissue signs and symptoms		
Acute and chronic pancreatitis		
Pancreatitis	2	0
Pancreatitis acute	4	1
Salivary gland disorders NEC		
Salivary hypersecretion	1	0
Stomatitis and ulceration		
Mouth ulceration	18	0
Stomatitis	2	0
Tongue disorders		
Glossitis	1	0
Tongue ulceration	2	0
Tongue signs and symptoms		
Glossodynia	1	0
Swollen tongue	9	0
Dental pain and sensation disorders		
Toothache	1	0
Oesophagitis (excl infective)		
Oesophagitis	1	0
Reflux oesophagitis	1	0
Gingival haemorrhages		

Gingival bleeding	1	0
Gastrointestinal disorders SOC Total	527	3

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
General disorders and administration site conditions		
Asthenic conditions		
Asthenia	2	0
Fatigue	13	0
Malaise	25	0
Body temperature altered		
Hypothermia	1	0
Death and sudden death		
Death	2	2
Febrile disorders		
Pyrexia	1	0
Gait disturbances		
Gait disturbance	4	0
Abasia	1	0
General signs and symptoms NEC		
Condition aggravated	1	0
Influenza like illness	3	0
Swelling	1	0
General physical health deterioration	1	0
Secretion discharge	1	0
Interactions		
Drug interaction	4	0
Mucosal findings abnormal		
Mucosa vesicle	1	0
Mucosal inflammation	1	0
Oedema NEC		
Face oedema	2	0
Oedema peripheral	7	0
Pain and discomfort NEC		
Chest discomfort	2	0
Chest pain	7	0
Facial pain	1	0
Pain	6	0
Therapeutic and nontherapeutic responses		

Drug ineffective	1	0
Feelings and sensations NEC		
Chills	1	0
Feeling abnormal	4	0
Feeling of body temperature change	1	0
General disorders and administration site conditions SOC Total	94	2

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Hepatobiliary disorders		
Cholestasis and jaundice		
Jaundice	2	0
Jaundice cholestatic	1	0
Hepatic failure and associated disorders		
Acute hepatic failure	2	1
Hepatic failure	1	0
Hepatobiliary signs and symptoms		
Hepatic pain	1	0
Hepatocellular damage and hepatitis NEC		
Hepatitis	9	0
Hepatitis acute	1	0
Hepatotoxicity	1	0
Hepatic and hepatobiliary disorders NEC		
Liver disorder	2	0
Liver injury	1	0
Hepatobiliary disorders SOC Total	21	1

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Immune system disorders		
Anaphylactic responses		
Anaphylactic reaction	1	0
Allergic conditions NEC		
Hypersensitivity	8	0
Immune and associated conditions NEC		
Decreased immune responsiveness	1	0
Immune system disorders SOC Total	10	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Infections and infestations		
Bacterial infections NEC		
Cellulitis	2	0
Bone and joint infections		
Bursitis infective	1	0
Candida infections		
Candidiasis	1	0
Vulvovaginal candidiasis	2	0
Clostridia infections		
Clostridium difficile colitis	1	0
Influenza viral infections		
Influenza	1	0
Lower respiratory tract and lung infections		
Lower respiratory tract infection	1	0
Pneumonia	1	0
Female reproductive tract infections		
Vaginal abscess	1	0
Skin structures and soft tissue infections		
Impetigo	2	0
Skin infection	1	0
Staphylococcal infections		
Staphylococcal scalded skin syndrome	1	0
Upper respiratory tract infections		
Pharyngitis	1	0
Rhinitis	1	0
Sinusitis	1	0
Urinary tract infections		
Kidney infection	1	0
Viral infections NEC		
Viral labyrinthitis	1	0
Vascular infections		
Lymphangitis	1	0
Infections and infestations SOC Total	21	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Injury, poisoning and procedural complications		
Fractures and dislocations NEC		
Joint dislocation	1	0
Skin injuries NEC		
Contusion	2	0
Non-site specific injuries NEC		
Fall	1	0
Non-site specific procedural complications		
Shunt occlusion	1	0
Overdoses		
Overdose	1	0
Site specific injuries NEC		
Head injury	1	0
Maladministrations		
Incorrect dose administered	2	0
Injury, poisoning and procedural complications SOC Total	9	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Investigations		
Carbohydrate tolerance analyses (incl diabetes)		
Blood glucose decreased	1	0
Blood glucose increased	1	0
Coagulation and bleeding analyses		
Coagulation time prolonged	6	0
International normalised ratio decreased	1	0
International normalised ratio increased	7	0
Prothrombin time prolonged	1	0
Liver function analyses		
Alanine aminotransferase increased	3	0
Blood bilirubin increased	3	0
Gamma-glutamyltransferase increased	1	0
Liver function test abnormal	17	0
Hepatic enzyme increased	2	0
Hepatic enzyme abnormal	1	0
Mineral and electrolyte analyses		
Blood sodium abnormal	1	0
Neurologic diagnostic procedures		
Glasgow coma scale abnormal	1	0
Physical examination procedures		
Body temperature increased	1	0
Platelet analyses		
Platelet count decreased	1	0
Urinalysis NEC		
Urine colour abnormal	1	0
White blood cell analyses		
White blood cell count increased	1	0
Investigations SOC Total	50	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Metabolism and nutrition disorders		
Appetite disorders		
Anorexia	3	0
Appetite disorder	1	0
Decreased appetite	1	0
Diabetes mellitus (incl subtypes)		
Diabetes mellitus inadequate control	1	0
Food malabsorption and intolerance syndromes (excl sugar intolerance)		
Fat intolerance	1	0
General nutritional disorders NEC		
Feeding disorder	1	0
Hypoglycaemic conditions NEC		
Hypoglycaemia	2	0
Total fluid volume decreased		
Dehydration	2	0
Metabolism and nutrition disorders SOC Total	12	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Musculoskeletal and connective tissue disorders		
Arthropathies NEC		
Arthritis	1	0
Bone related signs and symptoms		
Bone pain	1	0
Joint related signs and symptoms		
Arthralgia	8	0
Joint swelling	3	0
Musculoskeletal and connective tissue signs and symptoms NEC		
Muscle pains		
Myalgia	4	0
Muscle related signs and symptoms NEC		
Muscle spasms	2	0
Muscle twitching	1	0
Musculoskeletal and connective tissue pain and discomfort		
Back pain	6	0
Neck pain	1	0
Pain in extremity	3	0
Musculoskeletal and connective tissue disorders SOC Total	30	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Nervous system disorders		
Absence seizures		
Petit mal epilepsy	2	0
Central nervous system haemorrhages and cerebrovascular accidents		
Cerebral haemorrhage	2	1
Cerebrovascular accident	5	0
Haemorrhage intracranial	1	0
Cerebellar coordination and balance disturbances		
Coordination abnormal	1	0
Nystagmus	2	0
Disturbances in consciousness NEC		
Lethargy	6	0
Somnolence	4	0
Syncope	4	0
Dyskinesias and movement disorders NEC		
Dyskinesia	1	0
Psychomotor hyperactivity	3	0
Headaches NEC		
Headache	40	0
Tension headache	2	0
Memory loss (excl dementia)		
Amnesia	2	0
Mental impairment (excl dementia and memory loss)		
Disturbance in attention	2	0
Migraine headaches		
Migraine	2	0
Myelitis (incl infective)		
Myelitis transverse	1	0
Narcolepsy and hypersomnia		
Hypersomnia	1	0
Neurological signs and symptoms NEC		
Dizziness	21	0
Dizziness postural	2	0
Myoclonus	1	0

Neuromuscular disorders NEC		
Neuromyopathy	1	0
Paraesthesias and dysaesthesias		
Burning sensation	1	0
Paraesthesia	11	0
Partial complex seizures		
Complex partial seizures	1	0
Seizures and seizure disorders NEC		
Convulsion	14	0
Epilepsy	1	0
Sensory abnormalities NEC		
Ageusia	1	0
Dysgeusia	4	0
Hypoaesthesia	4	0
Sensory disturbance	3	0
Restless legs syndrome	1	0
Sleep disturbances NEC		
Poor quality sleep	1	0
Speech and language abnormalities		
Dysarthria	2	0
Tremor (excl congenital)		
Tremor	8	0
Nervous system disorders SOC Total	158	1

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Pregnancy, puerperium and perinatal conditions		
Abortions spontaneous		
Abortion spontaneous	1	0
Pregnancy, puerperium and perinatal conditions SOC Total	1	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Psychiatric disorders		
Abnormal behaviour NEC		
Breath holding	1	0
Abnormal behaviour	11	0
Affect alterations NEC		
Inappropriate affect	1	0
Affect lability	1	0
Anxiety symptoms		
Agitation	1	0
Anticipatory anxiety	1	0
Anxiety	9	0
Nervousness	1	0
Attention deficit and disruptive behaviour disorders		
Attention deficit/hyperactivity disorder	1	0
Behaviour and socialisation disturbances		
Aggression	3	0
Personality change	2	0
Social avoidant behaviour	1	0
Confusion and disorientation		
Confusional state	18	0
Disorientation	2	0
Deliria		
Delirium	6	0
Delusional symptoms		
Delusion	1	0
Persecutory delusion	1	0
Depressive disorders		
Depression	7	0
Depression suicidal	1	0
Dissociative states		
Dissociation	1	0
Disturbances in initiating and maintaining sleep		
Insomnia	23	0
Emotional and mood disturbances NEC		

Anger	3	0
Emotional disorder	1	0
Emotional distress	1	0
Frustration	1	0
Fluctuating mood symptoms		
Mood swings	2	0
Increased physical activity levels		
Restlessness	1	0
Mental disorders NEC		
Mental disorder	1	0
Mood alterations with depressive symptoms		
Depressed mood	5	0
Tearfulness	2	0
Mood disorders NEC		
Apathy	1	0
Parasomnias		
Abnormal dreams	8	0
Nightmare	18	0
Sleep terror	4	0
Somnambulism	1	0
Perception disturbances		
Hallucination	33	0
Hallucination, auditory	2	0
Hallucination, visual	8	0
Hallucinations, mixed	2	0
Personality disorders with dramatic behaviour (Cluster B)		
Histrionic personality disorder	1	0
Psychiatric symptoms NEC		
Psychiatric symptom	2	0
Psychotic disorder NEC		
Acute psychosis	1	0
Psychotic disorder	4	0
Sleep disorders NEC		
Sleep disorder	4	0
Somatoform disorders		
Conversion disorder	1	0
Speech articulation and rhythm disturbances		
Screaming	1	0
Dysphemia	1	0
Suicidal and self-injurious behaviour		
Suicidal ideation	2	0

Suicide attempt	1	0
Thinking disturbances		
Illogical thinking	1	0
Thinking abnormal	1	0
Panic attacks and disorders		
Panic attack	4	0
Panic reaction	1	0
Psychiatric disorders SOC Total	212	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Renal and urinary disorders		
Urinary abnormalities		
Chromaturia	3	0
Haematuria	1	0
Bladder and urethral symptoms		
Dysuria	2	0
Pollakiuria	1	0
Urinary retention	1	0
Renal failure and impairment		
Renal failure acute	3	0
Renal impairment	1	0
Urinary tract signs and symptoms NEC		
Renal pain	1	0
Renal and urinary disorders SOC Total	13	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Reproductive system and breast disorders		
Erection and ejaculation conditions and disorders		
Erectile dysfunction	1	0
Menstruation and uterine bleeding NEC		
Menstrual disorder	1	0
Metrorrhagia	1	0
Menstruation with decreased bleeding		
Menstruation delayed	1	0
Menstruation with increased bleeding		
Polymenorrhoea	1	0
Reproductive tract signs and symptoms NEC		
Genital rash	1	0
Vulvovaginal disorders NEC		
Vaginal haemorrhage	1	0
Vulval ulceration	1	0
Breast signs and symptoms		
Breast pain	1	0
Reproductive system and breast disorders SOC Total	9	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Respiratory, thoracic and mediastinal disorders		
Breathing abnormalities		
Dyspnoea	6	0
Hypoventilation	1	0
Bronchospasm and obstruction		
Asthma	2	0
Wheezing	2	0
Coughing and associated symptoms		
Cough	1	0
Productive cough	1	0
Lower respiratory tract inflammatory and immunologic conditions		
Pneumonitis	1	0
Nasal disorders NEC		
Epistaxis	16	0
Pharyngeal disorders (excl infections and neoplasms)		
Pharyngeal oedema	1	0
Pharyngeal inflammation	1	0
Upper respiratory tract signs and symptoms		
Throat irritation	1	0
Oropharyngeal blistering	1	0
Oropharyngeal pain	3	0
Respiratory tract disorders NEC		
Respiratory disorder	1	0
Respiratory, thoracic and mediastinal disorders SOC Total	38	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Skin and subcutaneous tissue disorders		
Acnes		
Dermatitis acneiform	3	0
Alopecias		
Alopecia	2	0
Angioedemas		
Angioedema	2	0
Apocrine and eccrine gland disorders		
Cold sweat	3	0
Heat rash	1	0
Hyperhidrosis	4	0
Night sweats	3	0
Bullous conditions		
Blister	9	0
Dermatitis bullous	3	0
Erythema multiforme	4	0
Stevens-Johnson syndrome	4	0
Toxic epidermal necrolysis	2	0
Dermal and epidermal conditions NEC		
Scab	1	0
Skin discolouration	1	0
Skin discomfort	1	0
Skin disorder	1	0
Skin reaction	2	0
Swelling face	13	0
Hypoaesthesia facial	1	0
Dermatitis and eczema		
Dermatitis allergic	8	0
Dermatitis diaper	1	0
Eczema	2	0
Erythemas		
Erythema	11	0
Rash erythematous	15	0
Exfoliative conditions		

Skin exfoliation	4	0
Panniculitides		
Erythema nodosum	2	0
Papulosquamous conditions		
Rash papular	8	0
Photosensitivity conditions		
Photosensitivity reaction	1	0
Purpura and related conditions		
Petechiae	1	0
Purpura	3	0
Skin injuries and mechanical dermatoses		
Skin chapped	1	0
Skin vasculitides		
Vasculitic rash	2	0
Urticarias		
Urticaria	18	0
Pruritus NEC		
Pruritus	12	0
Rash pruritic	15	0
Pruritus generalised	10	0
Rashes, eruptions and exanthems NEC		
Rash	85	0
Rash generalised	30	0
Rash macular	18	0
Rash maculo-papular	12	0
Skin and subcutaneous tissue disorders SOC Total	319	0

Drug Analysis Print
Drug Name: Tamiflu

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Vascular disorders		
Circulatory collapse and shock		
Haemorrhages NEC		
Haematoma	1	0
Vascular hypertensive disorders NEC		
Hypertension	2	0
Peripheral vascular disorders NEC		
Flushing	1	0
Hot flush	1	0
Vascular hypotensive disorders		
Hypotension	2	0
Site specific vascular disorders NEC		
Pallor	3	0
Vascular disorders SOC Total	10	0

Drug Analysis Print
Drug Name: Relenza

Run Date: 1 April 2009 to 5 November 2009		
Total number of reactions: 37	**Total number of ADR reports:** 19	**Total number of fatal ADR reports:** 1

System Organ Class	Reactions	Fatal Reactions
Blood and lymphatic system disorders	2	0
Gastrointestinal disorders	3	0
General disorders and administration site conditions	4	0
Infections and infestations	1	0
Injury, poisoning and procedural complications	2	0
Investigations	1	0
Musculoskeletal and connective tissue disorders	4	0
Nervous system disorders	5	0
Pregnancy, puerperium and perinatal conditions	2	1
Respiratory, thoracic and mediastinal disorders	6	0
Skin and subcutaneous tissue disorders	6	0
Vascular disorders	1	0
Total	37	1

Glossary/Abbreviations

ADR - Adverse Drug Reaction

Age group - lists which age groups are included in the Drug Analysis Print - either ALL, Adolescent, Adult, Child, Elderly, Infant or Neonate

Data lock date - shows data on the database at this specified date and time

HLT - High Level Term - see definition of MedDRA

MEDRA - this stands for Medical Dictionary for Regulatory Activities, which is the internationally agreed list of terms used for Medicines Regulation. MedDRA groups related adverse drug reaction terms in a hierarchical structure whereby the 'preferred term' (PT) (e.g. tunnel vision) is grouped under the broader heading the 'high level term' (HLT) (e.g. visual field disorders). 'High level terms' are contained within the 'system organ class' (SOC) (e.g. eye disorders). The 'preferred term' is the most specific term on the Drug Analysis Print, while the 'system organ class' is the most general

Multi active constituent products - contain the drug constituent of interest plus one or more other drug constituents (e.g. co-codamol contains paracetamol and codeine)

NEC - appears in MedDRA and stands for Not Elsewhere Classified

NOS - appears in MedDRA and stands for Not Otherwise Specified

PBG - Product Brand Generic - this means drug brand name e.g. Amoxil is a PBG for the drug substance amoxic

Products included in this print - this is a list of the products for which at least one suspected Adverse Drug Reaction (ADR) report has been received that specifies that product as a 'suspected drug' (i.e. suspected causal association with the reaction). It does not provide an exhaustive list of the products which contain the named drug substance

PT - Preferred Term - see definition of MedDRA

Reaction - defines which ADRs are included in the Drug Analysis Print - either ALL, Serious or Non-Serious

Reporter type - lists the reporter types which are included in the Drug Analysis Print - either Patient, Health Professional or ALL (i.e. both)

Report run date - the date the Drug Analysis Print was produced

Route of admin - lists the route of administration of the suspect drug for which reports are included in the Drug Analysis Print, e.g. ORAL only includes reports where the suspect drug was specified as having been taken by the oral route, or ALL which includes all routes of administration

Spontaneous - suspected ADR reports sent in to the Yellow Card Scheme are called spontaneous reports

Single active constituent products - contain only the drug substance of interest

System Organ Class (SOC) - this is the highest level in MedDRA which groups together reactions that affect similar systems/organs in the body

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Blood and lymphatic system disorders		
Leukopenias NEC		
Lymphopenia	1	0
Neutropenias		
Neutropenia	1	0
Blood and lymphatic system disorders SOC Total	2	0

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Gastrointestinal disorders		
Diarrhoea (excl infective)		
Diarrhoea	1	0
Nausea and vomiting symptoms		
Nausea	1	0
Vomiting	1	0
Oral soft tissue signs and symptoms		
Gastrointestinal disorders SOC Total	3	0

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
General disorders and administration site conditions		
Asthenic conditions		
Fatigue	1	0
Death and sudden death		
General signs and symptoms NEC		
Pain and discomfort NEC		
Chest discomfort	1	0
Chest pain	1	0
Feelings and sensations NEC		
Feeling cold	1	0
General disorders and administration site conditions SOC Total	4	0

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Infections and infestations		
Urinary tract infections		
Kidney infection	1	0
Infections and infestations SOC Total	1	0

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Injury, poisoning and procedural complications		
Pregnancy related accidental exposures and injuries		
Drug exposure during pregnancy	2	0
Injury, poisoning and procedural complications SOC Total	2	0

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Investigations		
Coagulation and bleeding analyses		
International normalised ratio increased	1	0
Investigations SOC Total	1	0

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Musculoskeletal and connective tissue disorders		
Joint related signs and symptoms		
Arthralgia	1	0
Muscle pains		
Myalgia	1	0
Musculoskeletal and connective tissue pain and discomfort		
Neck pain	1	0
Pain in extremity	1	0
Musculoskeletal and connective tissue disorders SOC Total	4	0

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Nervous system disorders		
Headaches NEC		
Headache	1	0
Neurological signs and symptoms NEC		
Dizziness	2	0
Paraesthesias and dysaesthesias		
Paraesthesia	1	0
Speech and language abnormalities		
Dysarthria	1	0
Nervous system disorders SOC Total	5	0

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Pregnancy, puerperium and perinatal conditions		
Abortions spontaneous		
Abortion spontaneous	1	0
Stillbirth and foetal death		
Intra-uterine death	1	1
Pregnancy, puerperium and perinatal conditions SOC Total	2	1

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Respiratory, thoracic and mediastinal disorders		
Bronchospasm and obstruction		
Asthma	1	0
Bronchospasm	3	0
Wheezing	1	0
Upper respiratory tract signs and symptoms		
Oropharyngeal pain	1	0
Respiratory, thoracic and mediastinal disorders SOC Total	6	0

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Skin and subcutaneous tissue disorders		
Dermatitis and eczema		
Dermatitis allergic	1	0
Erythemas		
Rash erythematous	1	0
Urticarias		
Urticaria	1	0
Pruritus NEC		
Pruritus	1	0
Rash pruritic	1	0
Rashes, eruptions and exanthems NEC		
Rash generalised	1	0
Skin and subcutaneous tissue disorders SOC Total	6	0

Drug Analysis Print
Drug Name: Relenza

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Vascular disorders		
Circulatory collapse and shock		
Peripheral vascular disorders NEC		
Hot flush	1	0
Vascular disorders SOC Total	1	0