

# WHO Drug Information

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## **Announcement**

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**The 14th International Conference of Drug Regulatory Authorities (ICDRA) will be hosted by the Health Sciences Authority, Singapore, in collaboration with the World Health Organization**

**The ICDRA will take place in Singapore from 30 November to 3 December 2010**

**Updated information is available at:  
<http://www.icdra2010.sg>  
<http://www.who.int/medicines/icdra>**

# International Nonproprietary Names

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## INN identifiers for biological products

The International Nonproprietary Names (INN) Programme was created by WHO in the 1950s with the intention of providing convenient common names for pharmaceutical substances. At the time of its origin, as well as during its later development, the INN Programme was inherently linked to progress in drug research and its success was reliant on the ability to deal appropriately with each new group of medicinal products that entered into therapeutic use. In the 1980s, the development of biotechnology products based on recombinant techniques led to highly novel therapeutic agents, thus creating a new need for adaptation of the INN system. The present article describes the ways that the INN Programme has responded to the challenges that arose in connection with this evolution.

Basic rules for the INN system set the limits within which all INN can be constructed. They include the need to properly define the substance or product that is named, to indicate in the name the pharmacological or therapeutic class to which the substance or product belongs by use of the INN stem system and, finally, to shape the name in a manner which facilitates its use by prescribers. (These issues are summarized on page 274.)

In its initial phase, the INN Programme was designed to cover only single chemi-

cal substances of well-defined structure although other groups of non-homogenous established products, including from natural sources, were also considered. When substances which had already been named by the INN Programme became available through new biotechnological processes, earlier decisions on naming non-homogenous products had an influence on defining and naming novel products. Practices recognized in naming and defining two specific product groups: low molecular weight heparins and insulins strongly influenced this approach. (A discussion of these practices is found on page 274 and 275.)

Specific approaches are needed when formulating definitions and, in particular, for creating suitable INN for biotechnological products. These approaches have been under active consideration by the INN Programme since the 1980s and were finally formulated in a 1994 INN guideline (1). Until now, 45 INN with Greek letter identifiers have been selected for glycosylated biological products.

Application of the guidelines in naming of individual groups of biological products containing carbohydrate residues in their structure is described on pages 275–277. Difficulties that relate to the use of Greek letter identifiers in naming of interferons are presented on page 279. The naming of monoclonal antibodies (mAbs), an important group of glycoproteins obtained by biotechnology, is not considered in this document as issues related to mAb names have been discussed separately at recent INN meetings and are also reviewed in two issues of *WHO Drug Information* (2). Related documents of

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interest are also available on the INN website including a document on INN for biological and biotechnology substances (3), documents relating to biologicals and mAbs (4) and an INN document on biosimilars (5).

## Creating INN

In the selection of INN, two separate issues are considered which influence the final shape of the name: (i) the way in which the substance is identified, and (ii) the structure of the name.

In the case of individual chemical substances, the identification process is based on chemical names established by the International Union of Pure and Applied Chemistry (IUPAC). The chemical designation is further supported by a graphic formula.

In the case of products obtained by biotechnology, the identification process is more complicated because such products usually form a mixture (the word “complex” is sometimes used) of several (or more) individual substances of similar structure and activity. The use of these products occurs without separation into individual active components. Definition of such products is complicated and is made individually for each product group. Formulation of definitions has progressed in line with analytical methods that increasingly allow a highly precise description of the structure of individual components. Examples of such changes occurring for individual groups are presented later.

Creation of INN for single chemical substances involves selection of an appropriate stem indicating the expected activity (or the decision to select an INN outside the stem system) followed by additional elements (usually the prefix) to create a distinctive name. When an INN

is selected for an active moiety, while a salt or an ester are employed in practice, an INN system is used to create suitable two-word names.

However, creating INN for products obtained by biotechnology is a more complex process. While the selection of basic stems (-ase, -mab, -micin, -mycin, -poetin, etc.) can be carried out according to the normal INN system, the naming of individual components of each series requires specific decisions on the extent of supplementary information to be included in the name. Those issues may vary for individual groups, but the following remarks apply to all situations.

General rules for the construction of INN offer only a few options for introducing elements of additional information. In one-word names this can be done by insertion of specific infixes (or prefixes). Otherwise, inclusion of a second or even third word is necessary as in the case of INN names. This approach is also used when describing complexes with metals or radioactive elements. The second-word approach is used frequently for biological products when the second word consists of a spelled out Greek letter.

Other identifiers widely used in scientific texts like numerals (Arabic or Roman), single letters (Latin alphabet), or single Greek letters in the original script, are precluded in INN. The reason for this rule is that such elements of names could lead to confusion and mistakes when used on a medical prescription, as numerals are used also to describe the dose (or concentration) or the number of dosage units. Single letters may also be confused, especially in handwriting.

The rules indicated above are also applied when selecting names for biological products with a glycoprotein structure. This can sometimes create additional difficulties, and is described later.

## Selecting INN for natural and semisynthetic products

### INN for LMW heparins

Low molecular weight (LMW) heparins are products obtained from natural heparin by chemical reaction leading to depolymerization and various changes in structure. Natural heparin is a sulfated polysaccharide (polyuronic acid), which is a mixture of components differing in chain length. LMW heparins also form mixtures of individual components that may differ in chain length and other structural features because they are produced from a natural heterogenous material by processes that do not warrant full homogeneity of the final product.

In 1983, when the first INN request for a LMW heparin was made, the INN Expert Group held prolonged discussions on whether this type of biological product should be included in INN system. It was concluded finally that selecting INN for such products would serve a useful purpose, and the stem *-parin* was selected for the group. The first name in the series was *enoxaparin* published in 1984. (The name was later modified to *enoxaparin sodium*.) The next group of requests for LMW heparins was given the INN *nadroparin calcium*, *parnaparin sodium*, *reviparin sodium* and *tinzaparin sodium*. Since then, a further eight INN containing the *-parin* stem have been selected.

As can be seen, individual members of the group are distinguished by using INN containing a common stem (*-parin*) and different prefixes. Individual products are defined in a rather complicated manner by description of manufacturing process, information on the structure of components and indication of molecular mass.

### INN for insulins

Insulin serves as an example of the approach for naming a group of related peptides by using a parent name (insulin)

followed (or preceded) by another word (or words) which is indicative of changes in the structure of the parent compound.

Insulin as such was never listed as an INN, being considered a well-established name. Between 1956 and 1958, INN were given to 6 insulin preparations: *insulin zinc suspension (crystalline)* and (*amorphous*), *protamine zinc insulin injection*, etc. The definition for each product described its preparation.

The first insulin obtained in 1982 by recombinant technology was given the INN *insulin human*, defined as "a protein having the normal structure of the natural antidiabetic principle produced by the human pancreas". In this case the second word in the name served a dual purpose, to link the actual structure of the product with that of a natural product, following the pattern established in the case of beef insulin and pork insulin.

The two-word approach was maintained for six further INN for modified insulins produced by biotechnology: *insulin argine*, *insulin lispro*, etc. containing modifications in the amino-acid sequences, but in these cases the second word serves to indicate a structural change. The substances are defined by describing their chemical structure.

### INN for erythropoietins

The first request for erythropoietin produced by biotechnology was made in 1988 by a US manufacturer. The request indicated that the substance was produced by "human clone  $\lambda$ HEPOFL13 protein moiety". The manufacturer's proposal to select erythropoietin as an INN was modified to eripoetin and this name was considered to be suitable provided that the product corresponded to the natural endogenous substance. It was also agreed that *-poetin* would be considered in the future as a stem for all erythropoietin type blood factors. Later in

1988 a second request for an INN for erythropoietin produced by biotechnology was received from another manufacturer.

However, during evaluation, the main problem that emerged concerning the recombinant form was that erythropoietin is a glycoprotein and that the activity of the substance depends strongly on the degree of glycosylation, as erythropoietin without the carbohydrate moiety is not active *in vivo*. Additionally, the recombinant forms differ in the type and degree of glycosylation and neither one is identical to the endogenous substance. Literature published on the subject confirmed that *N*-glycosylation is cell specific and site specific creating different glycoforms depending on the cell line used in the manufacturing process. It was also known that erythropoietin has three *N*-glycosylation sites at Asn<sup>24</sup>, Asn<sup>38</sup> and Asn<sup>83</sup> and one *O*-glycosylation site at Ser<sup>126</sup>. It was also known that carbohydrate moieties at *N*-terminals are quite complex (antennary structure).

On the basis of these arguments, the INN Group decided in 1989 to consider each request as representing a different product and to give an individual INN (6). Subsequently, the INN guideline adopted in 1994 (1) states that the Greek letter would serve to differentiate between compounds of the same amino acid sequence as human erythropoietin, which vary in the glycosylation pattern. INN for products with different amino acid sequence would be named using the -poetin stem and a random prefix (see *darbepoetin alfa*).

Between 1992 and 2007, six other INN were selected for erythropoietins produced by biotechnology: *epoetin gamma*, *epoetin delta*, *epoetin epsilon*, *epoetin zeta* (in Spanish *dseta*), *epoetin theta* (in Spanish *zeta*), *epoetin kappa*, and *epoetin omega*. In 2001, *darbepoetin alfa* was selected for an erythropoietin with a modified amino acid chain.

Definitions for all epoetins include information that the product is a 1-165-erythropoietin and contains a glycoform identifier expressed as  $\alpha$ ,  $\beta$  and  $\gamma$ , etc. In addition, definitions of *epoetin alfa*, *epoetin beta*, *epoetin gamma*, *epoetin epsilon* and *epoetin omega* also indicate the designation “human clone  $\lambda$ HEPOFL13 protein moiety” describing the gene coding of the amino acid sequence for human erythropoietin (HEPOFL being an abbreviation for Human Erythropoietin Fetal Liver source).

Definitions for three other epoetins include gene codes which are not in line with symbols used in regular gene nomenclature and are seemingly suggestions from manufacturers. The definition of *epoetin delta* contains the expression “human HMR4396” where the designation HMR4396 is the manufacturer’s code. A similar situation occurred in the case of *epoetin kappa*. In the case of *epoetin zeta*, the definition contains the expression “human clone B03XA01” where the designation B03XA01 is an ATC code for anti-anaemic preparations. It may be appropriate to later delete these designations from the definitions.

### INN for enzymes

INN for enzymes obtained from natural sources were usually selected to correspond to enzyme names established by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology. In those cases their structure was not further defined, but in the majority of cases the origin of the product was indicated. Recently, EC numbers have been added to the definitions.

The following examples show approaches that were used in this group of products. INN *urokinase* (published in 1966) was defined originally as “plasminogen activator isolated from human urine”, but the definition was changed in 1982 to “plas-

minogen activator isolated from human sources” to take account of the fact that the product started to be produced by human kidney cell culture *in vitro*. *Penicillinase* was defined as an enzyme obtained by fermentation from cultures of *Bacillus cereus*. *Kallidinogenase* was defined as an enzyme isolated from the pancreas or urine of mammals. *Sfericase* was defined as alkaline *Bacillus sphericus* proteinase.

In the 1990s, the situation progressed further when some specific enzymes that are glycoproteins started to be produced by biotechnology. The INN Group considered it necessary to indicate the glycoform by using the Greek letter system and a few examples are given here. INN *dornase alfa*, selected in 1993, was defined as “deoxyribonuclease (human clone 18-1 protein moiety)”. *Alglucosidase alfa* was defined as “human lysosomal prepro- $\alpha$ -glucosidase-(57-952)-peptide 199-arginine-223-histidine variant”. *Bucelipase alfa* was defined as “human bile-salt-activated lipase (cholesterol esterase, EC 3.1.1.13), glycoform alfa (recombinant hBSSL)”.

The use of Greek letters as identifiers was useful in the case of INN for  $\alpha$ -galactosidase. *Agalsidase alfa* was selected for a product isolated from recombinant human cell line and INN agalsidase beta for a product obtained from a Chinese Hamster Ovary (CHO) cell line. The same approach was used for *conestat alfa* which was selected in 2007 for a specific C1 esterase inhibitor (serine protease inhibitor).

A rather different situation occurred in the group of plasminogen activators. Initial discussion on these products was held in April 1985 (7). The first request for a tissue plasminogen activator was made in 1985 for a recombinant product for which *alteplase* was finally selected in 1988. Another one, for urokinase-type recom-

binant plasminogen activator followed, for which *saruplase* was selected in 1987. During the period 1985–1987 discussions were centred on the suitability of treating these products as enzymes by using the -ase suffix, and the issue of glycosylation was not considered. Finally, two stems for plasminogen activators: -teplase (for tissue-type) and -uplase (for urokinase-type) were established in 1987 (8).

As this decision was made before the system of glycoform identifiers was introduced, subsequent INN containing -plase stems were selected without this identifier, as in the majority of cases the INN were given for products with modifications in the amino acid chain. In some definitions the notion that the product is a glycoprotein was included in the definition. *Silteplase* was defined as “*N*[(*N*<sup>2</sup>-(*N*-glycyl-*N*-alanyl)-L-arginyl)plasminogen activator (human tissue-type protein moiety reduced), glycoform”. A similar remark was made in the definition for *nateplase* where “glycoform  $\beta$ ” is mentioned.

However, the absence of a glycosylation identifier later created a specific difficulty in the group of urokinase-type plasminogen activators. *Nasaruplase* was defined as “prourokinase (enzyme-activating) (human clone pA3/pD2/pF1) protein moiety”. This definition was later modified by adding “glycosylated”. At the same time *saruplase* — defined originally as “prourokinase (enzyme-activating) (human clone pUK4/pUK18 protein moiety reduced) — had to be changed by addition of “non-glycosylated”. In 2001, when another request was made for recombinant prourokinase produced by another cell line, *nasaruplase beta* was selected, defined as “prourokinase (enzyme-activating) human (clone pUK4/pUK18 protein moiety), glycosylated (murine cell line SP2/0)”. The use of a Greek letter identifier permitted a better separation of products differing in glycosylation patterns.

## INN for other glycosylated biologicals

Production of biological products identical or analogous to natural proteins or glycoproteins by recombinant technology was also applied to other types of products. The naming system used for creating INN for these products is similar to that already discussed.

### Blood coagulation factors and related products

In the group of blood coagulation factors (substances that are glycoproteins), the first INN requests for products obtained by biotechnology were made in 1993 for three products: blood coagulation factor VIIA, blood coagulation factor VIII and for blood coagulation factor VIII with a modified (truncated) amino acid structure.

The main issue centred on whether to retain the established descriptive names for products obtained by biotechnology or switch to the INN approach of one-word names composed of a suitable stem and a random prefix. The option that was finally accepted is reflected in the following policy statements:

- New names will only be given to products produced by recombinant biotechnology, but not to plasma derived products.
- Suitable stems will be created, glycosylation pattern may be reflected by addition of a Greek letter (spelled out).
- The distinction between natural and modified amino acid sequence will be indicated by using different prefixes.

This system was referred to as the “epoetin approach” (1).

INN *eptacog alfa* (activated) was selected in 1994 and defined as “blood coagulation factor VII (human clone λHVII2463 protein moiety). *Moroctocog alfa* was

defined as “(1-724)-(1637–1648)-blood coagulation factor VIII (human reduced) with 1649-2332- blood coagulation factor VIII (human reduced)”. *Octocog alfa* was defined as “blood coagulation factor VIII (human), glycoform α”. Other INN in the blood coagulation factor group include *beroctocog alfa*, *eptacog alfa pegol* (activated), *nonacog alfa*, and *vatreptacog alfa* (activated).

INN were also selected for two blood coagulation cascade inhibitors: *drotrecogin alfa* (activated) and *taneptacogin alfa*, and for five further products related to blood coagulation processes: *thrombin alfa*, *antithrombin alfa*, *troplasinogen alfa*, *thrombomodulin alfa*, and *so-thrombomodulin alfa*.

### Interleukins

The first INN in this group, *teceleukin*, was selected in 1985 for *N*-L-methionyl-interleukin-2 obtained by biotechnology. Subsequently, *aldesleukin* was selected in 1990 and *celmoleukin* in 1991 for interleukin-2 derivatives with modifications in the amino acid chain. Although natural interleukin-2 is a glycoprotein, the issue of glycosylation was not discussed at that time.

In 1994, the situation changed when a request was received for a derivative of interleukin-6. For this product, *atexakin alfa* was selected and defined as “1-(1-L-alanyl-L-proline)interleukin-6 (human clone HGF-15 protein moiety reduced), cyclic (54->50), (73->83)-bis(disulfide)”.

The formal decision to publish INN for glycosylated interleukins with a Greek letter in accordance with the general policy of naming glycosylated proteins was later confirmed in 1995 (10).

Following this decision, *edodekin alfa* was selected in 1998 for interleukin-12 and *adargileukin alfa* in 2003 for partially glycosylated modified interleukin-2.

*Tadekinig alfa* was selected in 2004 for interleukin-18 binding protein.

### Pituitary and placental glycoprotein hormones

Preparations produced from human postmenopausal urine containing a mixture of follicle-stimulating pituitary hormone (FSH) and luteinizing hormone (LH) have been manufactured since the 1960s and pINN *menotrophin* and *follotrophin (human)* were selected in 1963 and 1965. These INN were later withdrawn, as their definitions were considered not suitable. However, the issue was revisited in 1987 when *urofollitropin* was selected for a product defined as “a preparation of menopausal gonadotrophin extracted from human urine but possessing negligible LH activity”.

In 1991, a request was received for human FSH produced by recombinant technology followed by a request for human LH also produced by biotechnology. After discussion, *follitropin alfa* and *lutropin alfa* were suggested as INN, with Greek letters indicating glycosylation. This proposal was however contested, because natural pituitary hormones contain two amino acid chains in their structure that were designated by biochemists as  $\alpha$  and  $\beta$  subunits and these designations were widely used in the scientific literature. Although members of the INN Expert Group considered that the use of Greek letters in INN may lead to confusion, they conceded that such risk was minor (9).

The arguments against this selection may be of some relevance for scientists, but INN are intended primarily for use by health professionals such as physicians and pharmacists and not for scientists specialized in this area. As a result, *follitropin alfa* and *lutropin alfa* were selected as well as *follitropin beta*. *Corifollitropin alfa* was selected as a

fusion protein composed of FSH and 118-145-chorionic gonadotropin (human  $\beta$  subunit). Recently, *varfollitropin alfa* was selected as FSH with amino acid modifications in both subunits.

Other INN selected in this group for glycoprotein hormones obtained by biotechnology are *thyrotropin alfa* (thyrotropin releasing hormone) and *choriogonadotropin alfa* (human chorionic gonadotropin).

### Other glycoproteins

The Greek letter system was also employed for several other glycoproteins obtained by recombinant technology: *dibotermis alfa* and *eptotermis alfa* were selected for bone morphogenic proteins, *ismomultin alfa* was selected for cartilage glycoprotein 39, and *talactoferrin alfa* was selected for human lactoferrin.

### INN for interferons: difficulties with Greek letter identifiers

When discussing the use of Greek letter identifiers to indicate possible differences in the glycosylation pattern of glycoproteins it is necessary to mention also the case of INN interferon nomenclature, since, in the naming system used for this group of products, the Greek letters have a different meaning. A short review of this peculiar situation is thus necessary.

The INN *interferon* was selected in 1962 and defined as “a protein formed by the interaction of animal cells with viruses capable of conferring on animal cells resistance to virus infection”. The definition corresponded to the level of scientific knowledge at that time. Later developments have shown that this designation also covered substances produced by different types of cells. Three types of interferons were established: leukocyte interferon, fibroblast interferon and immune interferon, each type corresponding to a group of substances.

In 1982, the first INN request for leukocyte interferon produced by recombinant technology was received, followed in 1983 by a request for a fibroblast interferon. During discussions concerning interferon nomenclature, several options were considered. One was to create a stem -feron, but this was rejected due to conflicts with established trademarks for interferon preparations. Another approach was to follow designations currently used in biochemical literature: INF-a (for leukocyte interferons), INF-b (for fibroblast interferons) and INF-I (for immune interferons). The latter approach was provisionally agreed in April 1982 (10) together with the decision to spell out the Greek letter. This approach to interferon nomenclature was finally approved in 1984 (11) when *interferon alfa*, *interferon beta* and *interferon gamma* were selected with appropriate definitions.

The general definition for interferon alfa introduced the possibility of indicating protein variants in the name by hyphenated addition of an Arabic number. In the case of interferon alfa-2 further possibility of distinguishing substances that differ in amino acid composition at specific positions of the amino acid chain could be made by the addition of a small case Latin letter. The system was published in INN list PL52. Using this system *interferon alfacon-1* was selected in 1997, *peginterferon alfa-2a* and *peginterferon alfa-2b* in 2000 and *albinterferon alfa-2b* in 2008.

In interferon nomenclature, the Greek letter acquired a separate meaning, as it now identified the type of substance. The nomenclature also uses single letters and numbers, which is against normal INN practice. These differences are due to a decision by the INN Programme to follow the system established by the Interferon Nomenclature Committee [later renamed Nomenclature Committee of the International Society for Interferon and Cytokine

Research (ISICR)]. In the 1980s, interferons were considered to be a highly important field of therapeutic progress, and the INN Programme considered that it was preferable to follow biochemical interferon nomenclature extensively used at that time, and thereby ignoring divergence with established rules for creating INN.

## Conclusion

As shown, the INN Programme has skilfully responded to the demand for selection and naming of new groups of therapeutic products and, in particular, those manufactured by recombinant technology. The INN system has found ways for naming these products either by linkage to customary names for older biological products and/or creating appropriate names for newer members of each series.

The INN Programme has also been challenged with developing appropriate ways for defining products composed of mixtures of closely related components and to gradually upgrade the definitions in response to the enormous progress in elucidation of the structure of biological substances.

This daunting task has required the use of individual approaches while taking into account the specificity of each group. To the extent possible, a common style of coining INN nomenclature has evolved, especially for products with the glycoprotein structure, where the use of Greek letter identifiers is now firmly established and is confirmed by the use of these identifiers in 45 INN to date.

## References

1. Report of the Twenty-fourth INN Consultation held in 1994. (See also reference 3: items 3.4 and 4.8.)
2. World Health Organization. *WHO Drug Information*, **22**(2) (2008) and **23**(3) (2009).

3. World Health Organization. [http://www.who.int/medicines/services/inn/CompleteBioRevDoc%2008-11-07\\_2\\_.pdf](http://www.who.int/medicines/services/inn/CompleteBioRevDoc%2008-11-07_2_.pdf)

4. World Health Organization. <http://www.who.int/medicines/services/inn/publication/en/index.html>

5. World Health Organization. [http://www.who.int/medicines/services/inn/BiosimilarsINN\\_Report.pdf](http://www.who.int/medicines/services/inn/BiosimilarsINN_Report.pdf)

6. Report of the Twentieth INN Consultation held in April 1990.

7. Report of the Fifteenth INN Consultation held in April 1985.

8. Report of the Seventeenth INN Consultation held in 1987.

9. Report of the Twenty-fifth INN Consultation held in April 1995.

10. Report of the Twelfth INN Consultation held in April 1982.

11. Report of the Fourteenth INN Consultation held in 1984.

# Safety and Efficacy Issues

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## Rituximab: multifocal leuko-encephalopathy

**Canada** — Healthcare professionals have been informed of important new safety information regarding the use of rituximab (Rituxan®) and progressive multifocal leuko-encephalopathy (PML).

Rituximab is authorized for the treatment of B-cell non-Hodgkin lymphoma (NHL), previously untreated B-cell chronic lymphocytic leukaemia (B-CLL), stage B or C, and rheumatoid arthritis in combination with methotrexate to reduce signs and symptoms in adult patients with moderate to severe rheumatoid arthritis who have had an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies.

This is the first case of PML in a patient with rheumatoid arthritis who has not been previously treated with other potent biologic immunomodulating therapies. Previously, two fatal cases of confirmed PML were reported in patients with rheumatoid arthritis treated with rituximab.

Physicians should consider PML in any patient being treated with rituximab who presents with new onset neurologic manifestations (i.e., cognitive impairment, motor deficit, speech and vision impairment) and should be immediately referred for neurological consultation.

PML is a rare, progressive, demyelinating disease of the central nervous system that usually leads to death or severe disability. PML is caused by activation of the JC virus. JC virus resides in latent form in 40–80% of healthy adults. The

factors leading to activation of the latent infection are not fully understood. PML has been reported in HIV-positive patients, immunosuppressed cancer patients, transplantation patients and patients with auto-immune diseases, including RA. There are no known interventions that can reliably prevent or adequately treat PML.

**Reference:** Communication dated 21 October 2009 from Hoffmann-La Roche Limited at [http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/\\_2009/rituxan\\_5\\_hpc-cps-eng.php](http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/rituxan_5_hpc-cps-eng.php)

## Darbepoetin alfa: risk of stroke

**United States of America** — A study has been published in *the New England Journal of Medicine* raising safety concerns about darbepoetin alfa and the risk of stroke. Additionally, among patients with a history of cancer, 60 of 188 patients taking darbepoetin alfa died compared to 37 of 160 on placebo.

Anaemia is associated with an increased risk of cardiovascular and renal events among patients with type 2 diabetes and chronic kidney disease. Although darbepoetin alfa can effectively increase haemoglobin levels, its effect on clinical outcomes in these patients has been inadequately tested.

The study involved 4038 patients with diabetes, chronic kidney disease, and anaemia. Primary end points were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease.

During the study, death or a cardiovascular event occurred in 632 patients assigned to darbepoetin alfa and 602 patients assigned to placebo. Death or end-stage renal disease occurred in 652 patients assigned to darbepoetin alfa and 618 patients assigned to placebo. Fatal or nonfatal stroke occurred in 101 patients assigned to darbepoetin alfa and 53 patients assigned to placebo. There was only a modest improvement in patient-reported fatigue in the darbepoetin alfa group as compared with the placebo group.

Furthermore, the use of darbepoetin alfa in patients with diabetes, chronic kidney disease and moderate anaemia who were not undergoing dialysis did not reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event or death or a renal event) and was associated with an increased risk of stroke. For many persons involved in clinical decision making, this risk will outweigh the potential benefits.

**Reference:** TREAT Investigators. A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. *New England Journal of Medicine* 2009; **361**:2019–2032

## Vigabatrin and movement disorders

**United Kingdom** — Vigabatrin (Sabril®) is an anti-epileptic indicated, in combination with other anti-epileptics, for the treatment of patients with resistant partial epilepsy (with or without secondary generalization) who have not responded to or who are intolerant of all other appropriate drug combinations. Vigabatrin is also indicated as monotherapy in the treatment of infantile spasms (West syndrome).

Researchers in Finland first raised concerns about a risk of movement disorders (including dystonia, dyskinesia, and hypertonia) and brain abnormalities

on MRI (interpreted as cytotoxic oedema) associated with the use of vigabatrin, after they received reports of these adverse drug reactions from a Finnish healthcare professional.

A Europe-wide review completed in July 2009 involving experts in paediatric neurology from the UK assessed the evidence available on this issue, including preclinical data, clinical data, reported cases of adverse drug reactions, and relevant published literature.

Clinical trial data (1) for vigabatrin in infantile spasms provide evidence of brain MRI abnormalities at all doses, but in particular in young infants treated with high doses ( $\geq 125$  mg/kg/day). These MRI abnormalities were transient, seemed to be dose dependent, and in most patients resolved even if treatment with vigabatrin continued.

The review concluded that it is not possible to correlate the MRI findings with the movement disorders based on the current data. Therefore, the two events of movement disorders and brain MRI abnormalities will be independently described in the updated product information for vigabatrin to reflect these new data. If new movement disorders occur during treatment with vigabatrin, consideration should be given to dose reduction or a gradual discontinuation of treatment in consultation with specialist advice.

**Reference:** Medicines and Healthcare Products Regulatory Agency. *Drug Safety Update*, Volume 3, Issue 4 November 2009.

## Alendronate: risk of low-energy femoral shaft fracture

**New Zealand** — A number of published case reports have described atypical low energy stress fractures of the subtrochanteric and proximal femoral shaft in patients taking alendronate long-term (1–3). In some cases, the patient experi-

enced prodromal pain in the affected area weeks to months before a complete fracture occurred.

Prescribers should consider the risk of atypical stress fractures in alendronate-treated patients reporting pain of the subtrochanteric or proximal femoral shaft. It is important to note that the reported alendronate-associated fractures were frequently bilateral; therefore the contralateral femur should be examined if a fracture is suspected.

Factors which may increase the risk of fractures include: vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, and chronic alcohol abuse.

It is important to note that atypical stress fractures have also been reported in patients not taking bisphosphonates. In addition, it is possible that other bisphosphonates may be associated with an increased risk of atypical stress fractures. Medsafe advises that the interruption of bisphosphonate therapy in patients with atypical stress fractures should only be considered following an individual risk-benefit assessment.

## References

1. Kwek EB, Goh K, Koh JSB, Png MA et al. An emerging pattern of subtrochanteric stress fractures: A long-term complication of alendronate therapy. *Injury* 2008;**39**: 224–231.
2. Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *New England Journal of Medicine* 2008;**358**(12): 1304–6.
3. Neviasser AS, Lane JM, Lenart BA et al. Low energy femoral shaft fractures associated with alendronate use. *Journal of Orthopaedic Trauma* 2008;**22**:346–50.

4. *Prescriber Update* 2009;**30**(4):25 November 2009 at <http://www.medsafe.nz>

## Ceftriaxone and calcium containing solutions

**Canada** — Healthcare professionals have been informed of updated prescribing information for ceftriaxone when used with calcium-containing solutions via the intravenous (IV) route. This new safety information is based on the results of two recent in vitro studies that showed an increased risk of ceftriaxone-calcium precipitates in neonatal plasma.

The following are new recommendations:

- Ceftriaxone is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.
- In patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.
- Diluents containing calcium, such as Ringer solution or Hartmann solution, are not to be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur.

Ceftriaxone is a long-acting broad spectrum cephalosporin antibiotic for paren-

teral use. Ceftriaxone is indicated for the treatment of lower respiratory tract infections, urinary tract infections, bacterial septicaemia, skin and skin structure infections, bone and joint infections, intra-abdominal infections, and meningitis when caused by susceptible organisms. Ceftriaxone is also indicated for uncomplicated gonorrhoea and for prophylaxis of patients undergoing certain surgical procedures.

**Reference:** Health Advisory dated 15 October 2009 at [http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/\\_2009/rituxan\\_5\\_hpc-cps-eng.php](http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/rituxan_5_hpc-cps-eng.php)

## Etravirine: severe skin and hypersensitivity reactions

**Canada** — Healthcare professionals have been informed of important safety information regarding severe skin reactions in patients receiving combination therapy including etravirine (Intelence®) tablets. Specifically, there have been postmarketing reports of severe hypersensitivity reactions sometimes accompanied by hepatic failure, and a fatality due to toxic epidermal necrolysis.

Severe, potentially life-threatening and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.

Discontinue etravirine immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy

initiated. Delay in stopping etravirine treatment after the onset of severe rash may result in a life-threatening reaction.

Cases within clinical and postmarketing experience illustrate the importance of vigilance and familiarity with the signs and symptoms of severe skin rash and hypersensitivity reactions. In Phase III clinical trials, Grade 3 and 4 rashes were reported in 1.3 % of subjects receiving etravirine compared to 0.2 % of placebo subjects. A total of 2 % of HIV-1-infected patients receiving etravirine discontinued from Phase III trials due to rash. Rash occurred most commonly during the first six weeks of therapy.

**Reference:** Communication dated 15 October 2009 from Janssen-Ortho Inc. at [http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/\\_2009/rituxan\\_5\\_hpc-cps-eng.php](http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/rituxan_5_hpc-cps-eng.php)

## Oseltamivir phosphate: dosing risk

**Canada** — The manufacturer of oseltamivir (Tamiflu®) has informed healthcare professionals of important dosing and administration information regarding powder for oral suspension.

Oseltamivir is a viral neuraminidase inhibitor authorized for use in the treatment and prevention of uncomplicated acute illness due to influenza infection in adults and children above one year of age who have been symptomatic for no more than two days or have come in close contact with an infected individual. Health Canada has also issued an Interim Order in July 2009 expanding use of Tamiflu® as a treatment or prophylaxis for children less than one year of age for infection caused by the pandemic H1N1 2009 virus.

When dispensing commercially manufactured oseltamivir powder for oral suspension (12 mg/mL), pharmacists should ensure that the units of measure on the prescription instructions match the dosing

device provided (e.g., a device graduated in mg for a prescription in mg).

**Reference:** Communication from the manufacturer dated 13 October 2009 at <http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof>

## Safety signal: hyponatraemia

**New Zealand** — The Centre for Adverse Reactions Monitoring (CARM) has examined recent reports of hyponatraemia in its database.

Hyponatraemia, defined as plasma sodium < 135 mmol/L, is caused by a range of medicines and clinical conditions. Medicine-related hyponatraemia occurs most often in the elderly early in the course of treatment. The mechanism is most often a syndrome of inappropriate antidiuretic hormone secretion or renal loss.

Medicines most often implicated in recent reports to CARM are selective serotonin or noradrenaline reuptake inhibitors (SSRIs/SNRIs) and thiazide diuretics. Other medicines reported more than once in 2007 and 2008 were anticancer agents, proton pump inhibitors, sodium valproate and ACE inhibitor/diuretic combinations. Carbamazepine has also been frequently implicated in the database.

Serious hyponatraemia (plasma sodium < 120 mmol/L) can lead to confusion, convulsions and serious neurological damage. Examination of serious symptomatic reports to CARM revealed that in most cases more than one hyponatraemic medicine was implicated. The reports that CARM has received support current advice that plasma sodium should be measured shortly after starting potentially hyponatraemic medicines, especially SSRIs or diuretics. Measurements should be repeated both before and after adding another hyponatraemic medicine. If there is mild persistent hyponatraemia the addition of further medicines or the

development of clinical conditions that can decrease plasma sodium may lead to a more profound and symptomatic reaction.

**Reference:** *Prescriber Update* 2009;**30**(4):23 November 2009 at <http://www.medsafe.nz>

## Clopidogrel and omeprazole: reduced effectiveness

**United States of America** — The Food and Drug Administration (FDA) is alerting healthcare professionals to new safety information concerning an interaction between clopidogrel (Plavix®), an anti-clotting medication, and omeprazole (Prilosec/Prilosec OTC®), a proton pump inhibitor (PPI). New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole.

Omeprazole inhibits the drug metabolizing enzyme CYP2C19 which is responsible for the conversion of clopidogrel into its active metabolite. New studies compared the active metabolite and its effect on platelets in clopidogrel plus omeprazole versus clopidogrel alone. The effect of clopidogrel on platelets was reduced by as much as 47% in people receiving clopidogrel and omeprazole together.

Other drugs that are potent inhibitors of the CYP2C19 enzyme would be expected to have a similar effect and should be avoided in combination with clopidogrel. These include: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine. Since the level of inhibition among other PPIs varies, it is unknown to what extent other PPIs may interfere with clopidogrel. However, esomeprazole, a PPI that is a component of omeprazole,

inhibits CYP2C19 and should also be avoided in combination with clopidogrel.

Separating the dose of clopidogrel and omeprazole in time will not reduce drug interaction. Other drugs to avoid in combination with clopidogrel because they may have a similar interaction include: esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine.

**Reference:** Food and Drug Administration, Medwatch, 17 November 2009 at [http://www.fda.gov/Drugs/Drug\\_Safety](http://www.fda.gov/Drugs/Drug_Safety)

## Bisphosphonates: osteonecrosis of the jaw

**United Kingdom** — The risk of osteonecrosis of the jaw is greater for patients receiving intravenous bisphosphonates for cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget disease. All patients with cancer should have a dental check-up before bisphosphonate treatment. During treatment, patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling

Individual bisphosphonates with different indications can be used for:

- Prophylaxis and treatment of osteoporosis.
- Treatment of Paget disease.
- As a component of some cancer regimens, particularly for metastatic bone cancer and multiple myeloma.

A Europe-wide review has been completed on the risk of osteonecrosis of the jaw (ONJ) in association with the use of bisphosphonates. The review included data from the published literature, data

provided by Marketing Authorization Holders (experimental and preclinical studies, clinical trials, and postmarketing reports) and guidelines. The review also incorporated advice from a group of experts representing all areas of medicine where bisphosphonates are used, dentistry and bone surgery, and representatives of patient organizations.

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) reached conclusions on four main areas: definition and diagnosis of ONJ related to bisphosphonates, possible underlying pathophysiological mechanism(s), risk stratification, and risk minimization.

A patient may be considered to have ONJ related to bisphosphonates if all of the following three characteristics are present:

- Exposed or necrotic bone in the maxillo-facial region that has persisted for more than 8 weeks.
- No history of irradiation of the jaw.
- Current or previous treatment with a bisphosphonate.

**Reference:** Medicines and Healthcare Products Regulatory Agency. *Drug Safety Update*, Volume 3, Issue 4 November 2009 at <http://www.mhra.gov.uk>

## Intravenous promethazine: serious tissue injuries

**New Zealand** — Promethazine injection is highly caustic to the intima of blood vessels and surrounding tissues (1). Reports from the United States describe serious tissue reactions including thrombosis, nerve damage, tissue necrosis and gangrene in patients who have received intravenous promethazine. In rare cases, surgical intervention such as skin graft, fasciectomy or amputation has been

required (1, 2). In New Zealand, promethazine injection is approved for the treatment of vomiting, allergic reactions (including anaphylaxis) and to induce sedation.

After reviewing the published literature, assessing New Zealand case reports, and consulting with healthcare professionals, Medsafe has concluded that there remains a clinical need for intravenous promethazine in New Zealand. However, Medsafe recommends that intravenous promethazine should only be used if the benefits clearly outweigh the risks in each patient. This may include emergency situations (such as treatment of anaphylaxis) or situations where intramuscular or oral administration is contraindicated.

To maximize safe use, Medsafe has offered the following advice:

- Deep intramuscular injection is the preferred route of administration of promethazine injection.
- Promethazine must not be administered subcutaneously or intra-arterially.
- An alternative medicine should be considered if intravenous administration is required.
- Promethazine should be administered through large patent veins. Veins in the hand and wrist should be avoided if possible (1).
- If intravenous administration is required, the maximum recommended concentration is 25 mg/mL and the maximum recommended rate of administration is 25 mg/minute. Further dilution and administration over 10–15 minutes may reduce the risks even further (1).
- The injection should be stopped immediately if pain or a burning sensation occurs.

- Patients should be advised to seek medical assistance if pain, a burning sensation, swelling or blistering occurs at any time after the administration of intravenous promethazine.

The New Zealand data sheet for promethazine is currently being updated in line with this advice (4).

#### References

1. Grissiner M. Preventing serious tissue injury with intravenous promethazine (Phenergan®). *P&T* 2009;**34**(4):175-176.
2. FDA. Information for Health Professionals – Intravenous Promethazine and Severe Tissue Injury, Including Gangrene. 16 September 2009 at <http://www.fda.gov/Drugs>.
3. *Prescriber Update* 2009;**30**(4):23 November 2009 at <http://www.medsafe.nz>
4. Data sheet at <http://www.medsafe.co.nz/profs/Datasheet/dsform.asp>

### Cyproterone: risk of meningiomas

**United Kingdom** — Cyproterone acetate is a derivative of progesterone, and has progestagenic, antiandrogenic, and antigonadotrophic effects. High-dose preparations available in the UK include Cyprostat-50® and Cyprostat-100®, which are indicated for use in the treatment of prostate cancer. Cyproterone acetate is also available as Androcur-50®, which is indicated for the control of libido in men with severe hypersexuality or sexual deviation (or both). In some EU countries, Androcur-50® is used for the treatment of androgenization in women.

Lower-dose cyproterone acetate is available for use in women as co-cyprindiol (Dianette®) in combination with 35 micrograms ethinylestradiol for the treatment of severe acne that is refractory to prolonged antibiotic therapy, and for moderately severe hirsutism.

Meningiomas are the most common intracranial tumours, with an annual incidence of six per 100 000 in the general population. Multiple meningiomas account for approximately 1–10 % of all cases. Though histologically benign, they can have serious consequences. The potential role of sex hormones in the development of meningiomas has been postulated: approximately 70% of meningiomas express progesterone receptors and about 30% express oestrogen receptors (1). The occurrence of (multiple) meningiomas has been reported in association with longer-term use (years) of cyproterone acetate at doses of 25 mg/day or higher.

Up to September 2009, 36 cases of meningioma, of which 19 described multiple meningioma, have been reported worldwide in association with high-dose cyproterone acetate. Nine cases were discussed in a published case series, (2) and 27 cases are unpublished case reports. Duration of treatment with cyproterone acetate ranged from 4 to 27 years and in all but one case it was prescribed at doses higher than 25 mg per day. Thirty-one of the cases were from France (which compared with other countries has extensive use of high-dose cyproterone acetate). None of the reported cases had a fatal outcome.

Advice for healthcare professionals:

- Patients with existing meningioma or a history of meningioma must not be prescribed cyproterone acetate at doses of 25 mg per day or higher.
- This advice does not apply to medicines that contain low-dose cyproterone acetate such as co-cyprindiol (Dianette®).

#### References

1. Blitshteyn S et al. *J Clin Oncol* 2008; **26**: 279–82.

2. Froelich S et al. *Endocrine Abstracts*. Proceedings of the 10th European Congress of Endocrinology; Berlin, Germany. 2008; **16**:158. <http://www.endocrineabstracts.org>

3. *Drug Safety Update*. Volume 3 Issue 3, October 2009 at <http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON059804>

## Gadolinium-containing contrast agents

**European Union** — The European Medicines Agency (EMA) has adopted a set of recommendations aimed at minimizing the risk of nephrogenic systemic fibrosis (NSF) with gadolinium-containing contrast agents in patients at risk of developing the condition.

Gadolinium-containing contrast agents are used in patients undergoing magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA) scans. The Agency's Committee for Medicinal Products for Human Use (CHMP) reviewed these agents because of the association between the use of gadolinium-containing contrast agents and NSF, a rare, serious and sometimes life-threatening condition that is characterized by formation of connective tissues in the skin, joints, muscles and internal organs, in patients with severe kidney problems.

Based on currently available data, and with risk minimization measures in place, the CHMP considers that the balance of benefits and risks of these agents is acceptable.

#### References

1. European Medicines Agency makes recommendations to minimise risk of nephrogenic systemic fibrosis with gadolinium-containing contrast agents. Press Release, Doc. Ref. EMA/CHMP/739818/2009, 20 November 2009 at [www.emea.europa.eu](http://www.emea.europa.eu)

2. Question-and-answer document<<http://www.emea.europa.eu/pdfs/human/referral/gadolinium/72739909en.pdf>>.

3. A public statement on the association between gadolinium-containing contrast agents and the NSF. February 2007. <http://www.emea.europa.eu/pdfs/human/press/pus/4974107en.pdf>

## Cesium chloride: cardiac risks

**Canada** — Use of stable cesium compounds (non-radioactive form of cesium salts, primarily cesium chloride) may pose a risk of life-threatening heart problems. Cesium, primarily in the form of cesium chloride, is promoted on the Internet to prevent various forms of cancer and as a self-administered cancer treatment.

While use of radioactive cesium in radiation treatment for cancer is authorized in Canada, Health Canada has not authorized any health products containing stable cesium compounds for oral or intravenous use, including cesium chloride. However, numerous Internet sites promote the oral use of cesium chloride as an alternative to chemotherapy.

Health Canada is aware of three cases of serious cardiac arrhythmias (irregular heartbeat) in Canadian consumers who took oral cesium chloride. These patients also experienced decreased or loss of consciousness.

**Reference:** *Medeffect Health Advisory*, 10 September 2009 at <http://hc-sc.gc.ca>

## Washout or taper when switching antidepressants

**Australia** — Antidepressants are indicated for the treatment of major depressive disorders and may be indicated also for anxiety disorders, obsessive compulsive disorder, premenstrual dysphoric disorder and/or chronic pain. They include:

- Selective serotonin reuptake inhibitors (SSRI)
- Tricyclic antidepressants
- Noradrenergic and 5HT<sub>1</sub>-serotonergic receptor agonists
- Serotonin and noradrenaline reuptake inhibitors (SNRI)
- Noradrenaline reuptake inhibitors
- St John's Wort (*Hypericum perforatum*)

These drugs have various mechanisms of action but they share a number of similar properties which may predispose individuals to suffer from adverse effects due to interactions when switching antidepressants even if they are of the same class.

One of the more serious possible outcomes is the development of serotonin syndrome – a potentially life threatening condition caused by the accumulation of serotonin in the central nervous system (1–4). Serotonin syndrome is a potential adverse effect of all antidepressants and it can occur when treatment is not interrupted as well as during switching, particularly in the elderly (1,3,4).

The risk of serotonin syndrome increases if there is simultaneous exposure to more than one drug that can cause this syndrome. The Therapeutic Goods Administration (TGA) has received several reports describing this situation, some of which include life-threatening outcomes.

To avoid the possibility of an interaction, an appropriate washout period is required to substantially clear the first antidepressant from the body before the second is introduced. Unfortunately, no simple advice on the appropriate washout period can be given. In general, a drug is not completely cleared until a period equivalent to 4–5 half lives has elapsed after a

drug is ceased. The half life of antidepressants varies substantially from about two hours for citalopram and moclobemide and up to six days or more for fluoxetine, while the effect of irreversible MAOIs such as phenelzine can persist for several weeks after the drug has been ceased.

There are no set guidelines on switching amongst antidepressants and factors that should be considered will vary depending on the properties of the antidepressants and the patient's situation including the duration of time the patient has been on the first antidepressant, patient age, other medications and other health issues (5,6).

Useful information on antidepressant-free intervals when changing from one antidepressant to another is available in the Therapeutic Guidelines — Psychotropic Medicines and in the Australian Medicines Handbook (5,6).

*Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 28, Number 5, October 2009.*

## References

1. ADRAC. Serotonin syndrome. *Aust Adv Drug Reactions Bull* 2004; **23**(1).
2. ADRAC. Tramadol and serotonin syndrome. *Aust Adv Drug Reactions Bull* 2001; **20**(4).
3. ADRAC. Serotonin syndrome with duloxetine. *Aust Adv Drug Reactions Bull* 2009; **28**(4).
4. Isbister G, Buckley N, Whyte I. Serotonin toxicity: A practical approach to diagnosis and treatment. *MJA* 2007; **187**: 361-365.
5. Changing Antidepressants. *Australian Medicines Handbook* 2007, p 714.
6. *Therapeutic Guidelines. Psychotropic.* Version 6, 2008, pp 112-113.

## Zanamivir inhalation powder must not be nebulized

**Singapore** — Healthcare professionals have been informed of the death of a patient with influenza who received zanamivir (Relenza®) inhalation powder which was solubilized and administered by mechanical ventilation. The death was attributed to obstruction of the ventilator which could have been due to lactose in the formulation causing stickiness when the powder is mixed with the nebulizing solution.

The manufacturer wishes to highlight to healthcare professionals that Relenza® Inhalation Powder is not intended for reconstitution in any liquid formulation and is not recommended for use in any nebulizer or mechanical ventilator. Zanamivir for nebulization has not been approved by any regulatory authority and the safety, effectiveness and stability of zanamivir use by nebulization have not been established.

**Reference:** Health Sciences Authority (HSA). 14 October 2009. [http://www.hsa.gov.sg/publish/hsaportal/en/health\\_products\\_regulation/safety\\_information/DHCPL.html](http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/DHCPL.html)

## Pandemrix®: risk of fever

**European Union** — The European Medicines Agency (EMA) is warning that young children may experience fever after their second dose of the pandemic influenza vaccine Pandemrix®. Prescribers and parents should monitor the temperature of the vaccinated child and, if necessary, take measures to lower the fever (e.g., giving an antipyretic such as paracetamol). However, the Agency noted that the second dose increases the immune response against pandemic influenza.

The Agency has recommended that this information be included in the prescribing

information, and be taken into consideration when deciding whether to give a second dose to children.

**Reference:** *EMA Press Release*, Doc. Ref. EMEA/784404/2009 4 December 2009 at <http://www.emea.europa.eu/>

## **Weekly pandemic pharmacovigilance updates**

**European Union** — The European Medicines Agency (EMA) has published the first in a series of weekly pandemic pharmacovigilance updates.

These weekly bulletins will provide information on adverse reactions reported after the use of centrally authorized pandemic influenza vaccines and

antivirals in the European Union and complement the information the Agency has been publishing regularly on the development and approval of medicines for use during the pandemic.

This information will support European institutions and Member States in their communications, and provide an additional resource when recommending the use of vaccines and antiviral treatments.

The information on adverse reactions in the update comes from EudraVigilance, the central European database on adverse reactions, managed by the Agency.

**Reference:** *EMA Press Release*, Doc. Ref. EMEA/775140/2009 3 December 2009 at <http://www.emea.europa.eu/>

# Biomedicines and Vaccines

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## International biological standards: 2009 update

Innovation in biological medicines is occurring in more countries than ever before. In addition, the supply chain for biological medicines is increasingly complex and international in nature. Despite technological advances, controlling the quality, safety and efficacy of biologicals remains difficult and highly specialized. Therefore, strengthening biological standardization and its implementation, in particular in emerging economies, remains a fundamental function for WHO. The aim is to provide tools that will translate into appropriate oversight of new biologicals of potential public health benefit or oversight of biological components in the supply chain. Developing standards for quality, and associated reference materials through its Expert Committees and Expert Advisory Panels is a key priority for WHO.

The Expert Committee on Biological Standardization advises WHO on international biological standardization and key developments affecting the quality, safety and efficacy of vaccines, biological therapeutics, blood products and biological diagnostics. The Expert Committee met in Geneva from 19–23 October 2009 to enable WHO to fulfil one of its constitutional responsibilities to “*Develop, establish and promote international standards for biological products*”.

During its meeting, the Expert Committee established new WHO guidelines on the regulatory evaluation of “similar biotherapeutic medicines”. These products have a successful record in treating many life-threatening and chronic diseases. However, patients — particularly in developing

countries — have limited access to such medicines. The expiration of patents and/or data protection for the first major group of innovative biotherapeutics is ushering in an era of products “similar” to the originals, with the potential to significantly enhance accessibility. The guidance developed by WHO on appropriate regulation of this new class of products is in response to requests from many developing countries.

Revised WHO recommendations for the production and control of live attenuated influenza vaccine were established by the Expert Committee. The purpose of these recommendations is to provide vaccine manufacturers and national regulatory authorities with guidance that can be applied in developing specific processes for the production and control of human, live attenuated influenza vaccines. These recommendations are also intended to provide guidance on the nonclinical and clinical evaluation of influenza vaccines and apply to the production and control of influenza vaccines using embryonated hen’s eggs as substrates. The future possibility to produce human, live attenuated influenza vaccines using cell cultures as substrates is anticipated and, therefore, guidance is also provided for this eventuality. The recommendations with possible modifications apply to human, live attenuated influenza vaccines produced with seasonal vaccine strains for use during the interpandemic period as well as vaccines produced with strains for use during pandemics.

Infections caused by *Streptococcus pneumoniae* are responsible for substantial morbidity and mortality, particularly in the very young and elderly. Pneumococci are grouped into many serotypes (~ 91)

on the basis of their chemically and serologically distinct capsular polysaccharides. Certain serotypes are much more likely than others to be associated with clinically apparent infections, to cause severe invasive infections and to acquire resistance to one or more classes of antibacterial agents. The development of pneumococcal conjugate vaccines in which each of the selected bacterial capsular polysaccharides is coupled with a protein carrier molecule has been a major advance in the prevention of invasive pneumococcal disease (IPD).

Since 2006, WHO has recommended that all countries should incorporate pneumococcal conjugate vaccines in routine immunization schedules for children less than 2 years of age with prioritization of their introduction in countries with high child mortality rates and/or high rates of HIV infection. A 7-valent pneumococcal conjugate vaccine (7vPnC) that employs CRM197 as the carrier protein for all seven serotypes was the first to be developed. This vaccine was licensed in the USA in 2000 and subsequently has become available in approximately 90 countries worldwide. Pneumococcal conjugate vaccines that contain three or six serotypes in addition to those in the 7vPnC vaccine have recently become available in some countries. The 10-valent vaccine includes tetanus toxoid, diphtheria toxoid or a novel protein derived from nontypable *Haemophilus influenzae* (protein D) as the carrier proteins while the 13-valent vaccine uses only CRM197 as the carrier protein.

WHO recommendations for pneumococcal conjugate vaccine production and control were first established in 2003 (1). Since the 7vPnC vaccine was already approved in many countries, it was considered unethical to assess the protective efficacy of future pneumococcal conjugate vaccines in infants and toddlers in comparison to an unvacci-

nated control group. The recommendations discussed the design of immunogenicity studies to support licensure of new pneumococcal conjugate vaccines (including those containing conjugated capsular polysaccharides of serotypes additional to those in the 7vPnC vaccine) intended to prevent IPD and for administration to children aged less than 2 years. It was considered essential that the immunogenicity studies with a new pneumococcal conjugate vaccine should provide a link back to the vaccine efficacy against IPD that was demonstrated for the 7vPnC vaccine.

Therefore, it was recommended that immune responses to each serotype in the 7vPnC vaccine that is also included in a new pneumococcal conjugate vaccine should be directly compared in randomized clinical studies and that the primary comparison of immune responses should be based on serotype-specific IgG antibody concentrations measured by enzyme-linked immuno-sorbant assay (ELISA). In order to facilitate these comparisons a WHO reference ELISA assay was established that includes pre-adsorption of sera with pneumococcal C polysaccharide (C-PS) and serotype 22F polysaccharide.

Prompted by issues raised during the development of newer pneumococcal conjugate vaccines since the publication of the WHO 2003 recommendations (1), WHO held a consultation in 2008 to consider new scientific evidence and to discuss the need to provide revised guidance for manufacturers and licensing authorities. The Expert Committee on Biological Standardization has established a revised document that has been developed to take into account the most recent developments (2).

The Expert Committee also reviewed proposals to establish 24 new or replacement reference preparations as WHO

International Standards. International standards and biological reference preparations for use in the quality and safety control of biological products and in vitro diagnostic devices are submitted to the Expert Committee following validation of candidate preparations in global, coordinated studies.

Among the proposals, a reference panel covering the most prevalent hepatitis B genotypes worldwide was adopted to facilitate improvement of the quality of hepatitis B diagnostic devices and the traceability of test results between countries. Other reference materials for the control of the potency of blood products and the diagnosis of genetic diseases

were also adopted this year. These preparations are expected to be widely used by regulators, manufacturers and blood establishments worldwide and will support international regulations for blood products and the safety of blood products (2).

#### References

1. World Health Organization. Expert Committee on Biological Standardization. *Technical Report Series*, No. 927, annex 2 (2003).
2. Expert Committee on Biological Standardization: written standards and reference preparations; interim report. <http://www.who.int/biologicals>.

# International Harmonization

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## ICH Implementation: Quality Working Groups

In Brussels 2003, a new quality vision was agreed by parties of the International Conference on Harmonization (ICH) (1). This emphasized a risk and science-based approach to pharmaceuticals in an adequately implemented quality system. As a consequence, the guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality System (Q10) were drafted.

These concepts and principles depart from the traditional approaches to quality guidance, mainly based on end-product testing. Since it is important that proper implementation is strengthened by clarifying, explaining and removing ambiguities and uncertainties, an ICH Implementation Working Group (IWG) on ICH Q8, Q9 and Q10 has been formed and met during the recent ICH meeting held in Yokohama in June 2009. The IWG is drawn from the six member parties of the ICH: industry and medicines regulatory authorities of the European Union, Japan and United States of America (up to three experts per party). Observers to the ICH are allowed one expert and Interested Parties one expert each. The IWGs focus on the following issues:

### **Technical issues and related documentation**

- Common understanding of terminology.
- Interrelationship between Q8, Q9 and Q10.
- Applicability to both review and inspection.

- Final status after partial implementation is established (level of details in the dossier).

### **Additional implementation issues**

- Influence on existing ICH guidelines.

### **Communication and training**

- Questions and Answers, ICH briefing packs.
- External collaboration.
- Workshops.

The aim of the ICH Quality Implementation Working Group (Q-IWG) is to provide enhanced harmonized implementation training to industry and regulators in the three ICH regions. In addition, the group can offer opportunities to train colleagues in non-ICH regions. The newly designed standards workshop is planned to be conducted by those ICH experts who developed the ICH Q8, Q9 and Q10 guidelines and members of the ICH. These are intended to be the only workshops reviewed and referenced by the Q-IWG and will be conducted by the same faculty in all three ICH regions.

Training will cover the integrated use of ICH Q8, Q9 and Q10 guidelines and Q&A (question and answers) across the product life-cycle, from development to manufacturing and commercialization. Unlike other conferences and workshops on these topics, training will present a case study throughout the entire life-cycle from development to manufacturing and commercialization. Regulatory assessment and GMP inspection implementation aspects will be discussed. Furthermore,

**Status of additional ICH questions & answers** (*Supplementary table*)

	initial	adopted	open
General clarification	0	1	1
Quality by Design (QbD) topics	1		
• Design Space	6	2	
• Real Time Release Testing	8	3	3
• Control Strategy	3	1	1
Pharmaceutical Quality System	6	2	3
GMP Inspection practice	2	3	
Knowledge Management	4	1	
Software solution	1		
<b>Total</b>	<b>41</b>	<b>10</b>	<b>11</b>

learning opportunities will be provided for participants to practise in small groups the necessary skills for implementation of the guidelines.

Workshop deliverables will include materials to support understanding of integrated use of the concepts described in ICH Q8, Q9 and Q10 guidelines. These materials will be used by both regulators and industry to implement the three guidelines in their organizations.

If the ICH Global Cooperation Group (GCG) is organizing workshops outside an ICH region the Q-IWG will provide structure and content of the workshops. If WHO is organizing workshops, the Q-IWG can provide support.

The IWG is also looking into the availability of illustrative examples and case studies relevant to harmonized and consistent implementation. The initial goal was to reference existing material and develop examples and position papers.

A survey of conferences, publications and presentations has been carried out over the past six months. As a result, a list of relevant topics and activities was identified together with an analysis of specific needs for additional work. The review

demonstrated that there is a large amount of publications and workshops available covering ICH Q 8, Q9 and Q 10. The final consensus was that the Q-IWG should initiate, encourage and collaborate in the development of articles consistent with Q8, Q9, Q10 guidelines and the recently developed Questions and Answers.

**Reference:** ICH information available at <http://www.ich.org>

## ICH Pharmacopoeial Discussion Group

The Pharmacopoeial Discussion Group (PDG) [European Pharmacopoeia (PhEur), Japanese Pharmacopoeia (JP) and United States Pharmacopoeia (USP)] met in association with the Expert Working Groups of the International Conference on Harmonization (ICH), 8–12 June 2009 in Yokohama, Japan. The World Health Organization attended in its official capacity as observer.

Discussion focused on Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions. The ICH Q4B guideline was finalized (*Step 4*) on 1 November 2007.

This document describes a process for the evaluation and recommendation by the Q4B Expert Working Group (EWG) of selected pharmacopoeial texts to facilitate their recognition by regulatory authorities for use as interchangeable texts in the ICH regions. Following favourable evaluations, ICH will issue topic-specific annexes with information about these texts and their implementation (the Q4B Outcomes). Implementation of the Q4B annexes is intended to avoid redundant testing by industry.

Harmonization has been achieved by the PDG on nine of the ten General Chapters identified by the ICH Q6A Guideline. From those, eight have been evaluated in addition to two newly harmonized texts by the ICH Q4B Working Group as follows:

- Residue on Ignition/Sulphated Ash General Chapter (*ICH Q4B Annex 1*)
- Test for Extractable Volume of Parenteral Preparations General Chapter (*ICH Q4B Annex 2*)
- Test for Particulate Contamination: Sub-Visible Particles General Chapter (*ICH Q4B Annex 3, includes English JP text*)
- Microbial Enumeration Tests General Chapter (ICH Q4B Annex 4A)
- Tests for Specified Micro-organisms General Chapter (ICH Q4B Annex 4B)
- Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter (*ICH Q4B Annex 4C*)
- Disintegration Test (*ICH Q4B Annex 5, includes English JP text*)
- Uniformity of Dosage Units General Chapter (*ICH Q4B Annex 6*)
- Dissolution Test General Chapter (*ICH Q4B Annex 7*)

- Sterility Test General Chapter (*ICH Q4B Annex 8, includes English JP text*)
- Tablet Friability General Chapter (*ICH Q4B Annex 9*)
- Polyacrylamide Gel Electrophoresis General Chapter (*ICH Q4B Annex 10*).

ICH Q4B Annexes 1–5 and 8 have been signed off as ICH step 4 documents. Annexes 6 and 7 are pending feedback from PDG. Annex 9 and 10 are at the Step 2 stage.

PDG is working on the following general chapters within the harmonization process and they will be submitted for ICH Q4B evaluation upon final PDG sign off as being harmonized:

- Bulk and Tapped Density of Powders
- Analytical Sieving
- Capillary Electrophoresis
- Bacterial Endotoxin Test
- Colour Test (new method being reviewed).

Moreover, 26 of the 34 General Chapters and 40 of the 63 excipient monographs have been harmonized by PDG. In the course of indicating the harmonization statement in the three ICH pharmacopoeias, PDG has reviewed seven excipient monograph texts and identified typical discrepancies. A path to resolution has also been agreed that will facilitate further harmonization projects.

The possible implementation of these harmonized texts within the revision process of *The International Pharmacopoeia* will be reviewed by the forthcoming Forty-fourth WHO Expert Committee on Specifications for Pharmaceutical Preparations.

**Background: *The International Pharmacopoeia***

*The International Pharmacopoeia* comprises a collection of quality specifications for pharmaceutical substances (active ingredients and excipients) and dosage forms together with supporting general methods of analysis intended to serve as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements. *The International Pharmacopoeia*, or any part of it, may have legal status whenever a national or regional authority expressly introduces it into appropriate legislation.

Activities related to *The International Pharmacopoeia* are an essential element in the overall quality control and assurance of pharmaceuticals contributing to the safety and efficacy of medicines. The selection of monographs for inclusion in *The International Pharmacopoeia* recognizes the needs of specific disease

programmes and the essential medicines nominated under these programmes; it is based primarily on those substances included in the current WHO Model List of Essential Medicines.

Work on *The International Pharmacopoeia* is carried out in collaboration with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and with other specialists. The process involves consultation of and input from WHO Member States and drug regulatory authorities, WHO Collaborating Centres and national drug quality control laboratories in all six WHO regions, standard-setting organizations and parties, including regional and national pharmacopoeias and with manufacturers around the world. Clearly defined steps are followed in the development of new monographs.

# Prequalification of Medicines Programme

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## Prequalification of quality control laboratories

Increased availability and supply of good quality essential medicines for countries is an important component of the United Nations Millennium Development Goals. Unfortunately, several international funders and suppliers of essential medicines have faced difficulty in monitoring the quality of supplies in countries because of a lack of fully operational medicines quality control laboratories.

Given this situation, international donors and suppliers often preferred to have local medicine samples sent for analysis in quality control laboratories situated in Europe or North America. Such practices do not support sustainable development goals and are counter productive in building national capacity.

In collaboration with UNAIDS, UNICEF, UNFPA, the Global Fund, UNITAID, with support from the World Bank, WHO has set up a process to prequalify quality control laboratories that meet recommended international norms and standards for the analysis of medicines prequalified or being considered for prequalification by WHO.

As a first step, WHO has invited quality control laboratories in Africa to take part in the process. Laboratories were chosen based on their commitment to provide testing of pharmaceutical products for HIV/AIDS, tuberculosis and malaria (1). In September 2007, the scope of the procedure was extended and currently invitations are open to quality control laboratories in any region worldwide. WHO manages the assessment process and

identifies which quality control laboratories should be given priority based on need.

Participation in the prequalification process is described in *Procedures for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies* (2). For the time being, applying for and participation in the prequalification procedure is free of charge. However, the procedure also enables WHO to charge for the assessment of laboratories on a cost-recovery basis if the prequalification process is no longer funded by donors.

WHO assesses quality control laboratories through evaluation of preliminary information submitted by a laboratory and on-site inspection to assess compliance with the WHO guidelines on *Good Practices for National Pharmaceutical Control Laboratories* (3) and *Good Manufacturing Practices* (4). These and other related guidelines are published on the Prequalification Programme's web site (5). International Standard Organization (ISO) certification (ISO/IEC 17025) is also encouraged. If assessment demonstrates that a laboratory meets WHO recommended standards, it is included in the official List of WHO Prequalified Quality Control Laboratories that is considered acceptable for use by United Nations agencies or other interested parties (6).

Once a laboratory is included in the WHO List of Prequalified Quality Control Laboratories, ongoing monitoring of its activities is performed. This includes re-inspection at regular intervals, evaluation of results from participation in an appropriate proficiency testing scheme, and monitoring and investigation of any

Country	Region	Number of prequalified laboratories
Algeria	Africa	1
France	Europe	1
India	South-East Asia	1
Kenya	Africa	2
Morocco	Eastern Mediterranean	1
Singapore	Western Pacific	2
South Africa	Africa	2
Vietnam	Western Pacific	1

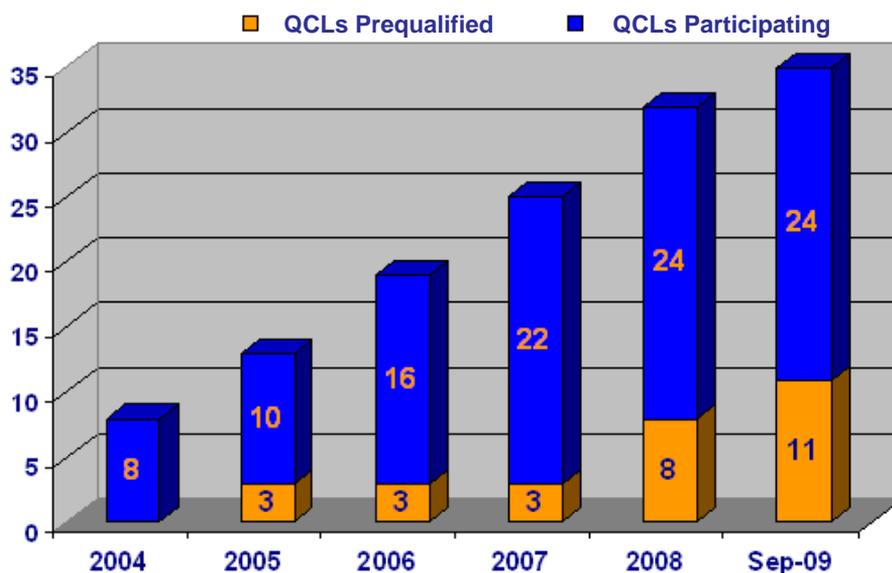
complaints concerning results of analysis or other service provided by the listed laboratories. To facilitate monitoring, each prequalified laboratory is requested to submit a brief annual report on its activities. An outline of the expected content of an annual report is available on the WHO web site (7).

A laboratory will be removed from the list if it is found that it no longer complies with the specified standards.

### Update on progress

As of October 2009, eleven laboratories have been prequalified by WHO. Five prequalified laboratories are located in the WHO Africa Region, three in the Western Pacific Region and one in each of the three regions: Eastern Mediterranean Region, Europe Region and South-east Asia Region. Apart from these eleven prequalified laboratories, there are twenty-four quality control laboratories participating in the procedure (See Table

**Table 1. Prequalification of quality control laboratories**



1). The majority of participating laboratories (26 of 35) are national quality control laboratories.

As part of the capacity building component of the WHO Prequalification of Medicines Programme, national quality control laboratories participating in the prequalification procedure are provided, if needed, with technical assistance in the form of a pre-audit or 1–3 week visit of an expert to the laboratory. The Programme also organizes training for national quality control laboratories and laboratories providing testing services to the government in the respective country.

### Inspections

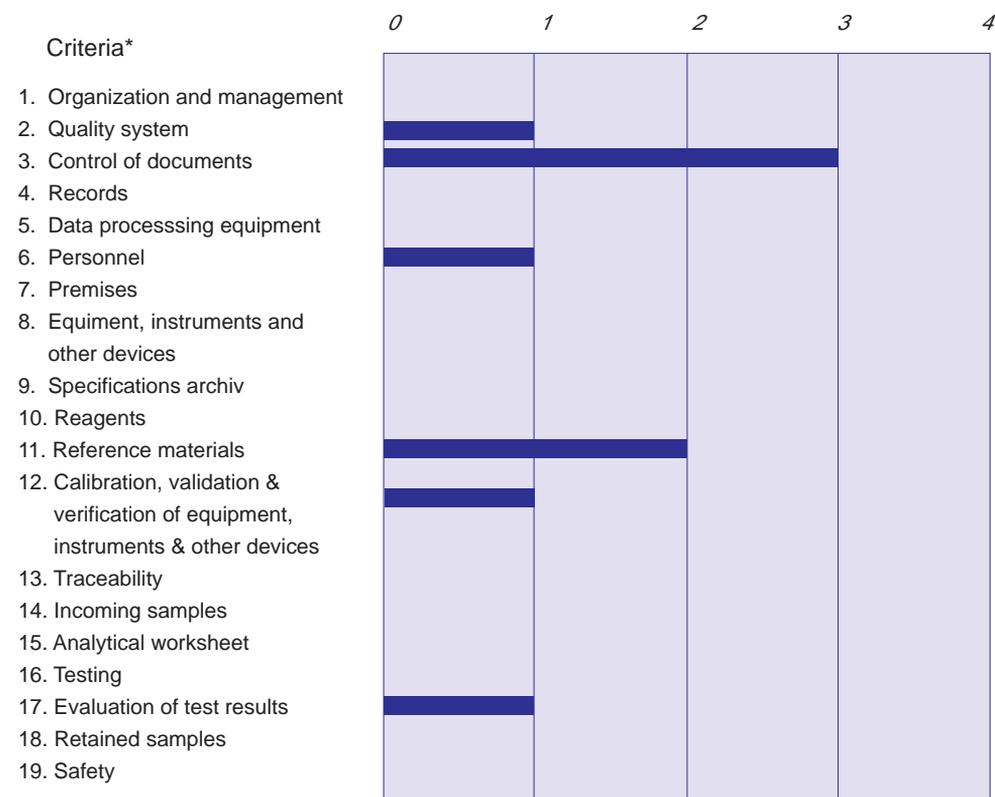
An inspection team is composed of a WHO prequalification inspector and a co-

inspector appointed by WHO from a member inspectorate of the Pharmaceutical Inspection Cooperation Scheme (PIC/S). An inspector (or inspectors) from the national medicines regulatory authority of the country in which the laboratory is located is invited to participate as an observer. Prequalified laboratories are re-inspected on a regular basis, usually every two to three years. Fourteen quality control laboratory inspections were carried out between March 2004 and September 2009.

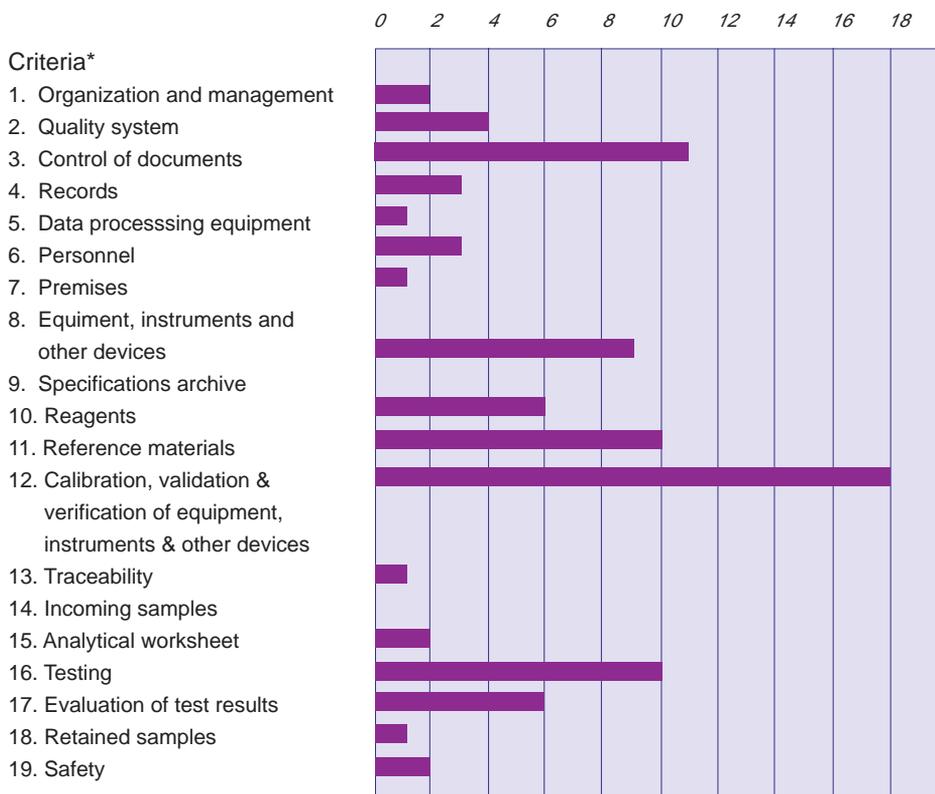
Over the years, the main observations of non-compliance during inspections include the following:

1. System of reference substances was insufficient in that:

**Figure 1. Cumulative number of critical observations from 14 inspections**



\* Refers to sections of WHO Good Practices for National Pharmaceutical Control Laboratories

**Figure 2. Cumulative number of major observations from 14 inspections**

\* Refers to sections of WHO Good Practices for National Pharmaceutical Control Laboratories

- Authorized written standard operating procedures for handling reference substances were not available, i.e.,
  - packing of working reference substances
  - labelling of working reference substances
  - acceptance criteria for working substances
- Inappropriate labelling of working standards
- Use of reference substances was not documented
- 2. Stocks of reagents and retention samples were not maintained under appropriate storage conditions.
- 3. The training system was insufficient in that:
  - Authorized written standard operating procedures for training were unavailable.
  - Training was not appropriately documented and assessed.
- 4. Authorized written standard operating procedures for internal audits were not available.

5. Reagents were not managed properly in that:

- Labels of some reagents did not specify shelf-life.
- Certificates of analysis were not available for all reagents.
- Reagents were not properly labelled.

6. Responsibilities, competencies and functions were not clearly defined in current job descriptions.

7. Computer software developed by the users was not appropriately validated or verified. Procedures were not established and implemented for protecting the integrity of data.

8. Authorized written standard operating procedures for the calibration of critical equipment were not available, i.e., HPLC, GC, dissolution and disintegration instruments. Equipment calibration and maintenance schedules were not available. Equipment not regularly qualified; IQ, OQ and prequalification protocols/reports were not available

9. Validation of microbiological laboratory autoclave was not conducted in accordance with current guidelines.

10. Pharmacopoeial test methods were not verified.

11. Out-of-specifications were not recorded and handled properly.

## References

1. World Health Organization. Prequalification of Medicines Programme. [http://www.who.int/prequal/info\\_applicants/eoi/EOI-QCLabsV3.pdf](http://www.who.int/prequal/info_applicants/eoi/EOI-QCLabsV3.pdf)
2. World Health Organization. Expert Committee on Specifications for Pharmaceutical Preparations. Annex 5: Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies. *Technical Report Series*, No. 943 (2007) at [http://www.who.int/prequal/info\\_general/documents/TRS943/TRS943.pdf#page=111](http://www.who.int/prequal/info_general/documents/TRS943/TRS943.pdf#page=111)
3. World Health Organization. Expert Committee on Specifications for Pharmaceutical Preparations. Annex 3: Good Practices for National Pharmaceutical Control Laboratories. *Technical Report Series*, No. 902 (2002). at [http://www.who.int/prequal/info\\_general/documents/TRS902/WHO\\_TRS\\_902.pdf#page=37](http://www.who.int/prequal/info_general/documents/TRS902/WHO_TRS_902.pdf#page=37)
4. World Health Organization. *Quality Assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Second updated edition. Good manufacturing practices and inspection* (2007). at [http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/production/en/index.html](http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html)
5. World Health Organization. Prequalification of Medicines Programme. [http://www.who.int/prequal/info\\_applicants/qclabs/prequal\\_quality\\_control\\_labs.htm](http://www.who.int/prequal/info_applicants/qclabs/prequal_quality_control_labs.htm)
6. World Health Organization. Prequalification of Medicines Programme. [http://www.who.int/prequal/lists/PQ\\_QCLabsList.pdf](http://www.who.int/prequal/lists/PQ_QCLabsList.pdf)
7. World Health Organization. Prequalification of Medicines Programme. [http://www.who.int/prequal/info\\_applicants/qclabs/Annual-Report\\_Labs.pdf](http://www.who.int/prequal/info_applicants/qclabs/Annual-Report_Labs.pdf)

# Pharmacovigilance Focus

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## **A/H1N1 vaccination safety: PaniFlow® surveillance tool**

PaniFlow® is a new software tool for reporting adverse events following immunization which is now being offered free to a number of countries in a joint Uppsala Monitoring Centre (UMC)/ World Health Organization (WHO) initiative.

In response to A/H1N1 pandemic influenza and plans for vaccination of large populations, safety issues are a prime concern. Most developed countries already have well-established systems for monitoring the safety of vaccination programmes and detecting problems.

PaniFlow® is a web-based data management software which allows vaccination programme staff to record all adverse events as they occur from any location with an Internet connection. This ensures continued reporting, even when infrastructure, like regular mail, is disrupted. Cumulative data is immediately available locally, nationally, and to the UMC where international patterns of events can be analysed and shared. Data can also be incorporated into the international WHO Global Individual Case Safety Report database (VigiBase®) managed by UMC. The software has search and analysis tools which permit issues and problems to be examined in all relevant parameters.

Individual countries can quickly detect potential safety problems in their own populations and take remedial action if causality is established. At UMC, the global picture can be rapidly reviewed and the international community alerted when problems are suspected or confirmed.

In an emergency situation, where the priority has been to secure supplies of vaccines and get them widely distributed, safety surveillance can sometimes take second place. As a result of multiple variables and uncertainties only comprehensive monitoring on a global scale can reveal the true, detailed picture of the impact of vaccination on individual patients and on public health. This is important also in a situation where safety concerns have been publicly expressed and/or the credibility of A/H1N1 vaccination challenged.

PaniFlow® is based on VigiFlow®, which is the programme used throughout the world by many members of the WHO Programme for International Drug Monitoring for managing and reporting adverse drug reactions. It is based on the software originally developed jointly by the Swiss national drug regulatory authority, Swissmedic, and UMC for use in Switzerland. Both programmes are uniquely designed to meet the needs of healthcare personnel and serve the interests of patient safety. While some training to use the programmes is needed, their user friendliness has been progressively improved and data entry itself is a simple task.

The first countries being offered free use of PaniFlow® by UMC are: Croatia, Lithuania, Morocco, Serbia, Sierra Leone, Togo and Turkey. All are countries with a track-record of reporting adverse events following immunization and are familiar with using VigiFlow®.

**Reference:** Uppsala Monitoring Centre at <http://www.who-umc.org>

# Regulatory Action and News

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## Influenza vaccines for 2010 southern hemisphere winter

**World Health Organization** — It is recommended that vaccines for use in the 2010 influenza season (southern hemisphere winter) contain the following:

- an A/California/7/2009 (H1N1)-like virus
- an A/Perth/16/2009 (H3N2)-like virus
- a B/Brisbane/60/2008-like virus.

**Reference:** *Weekly Epidemiological Record*, No. 41, 2009, 84, 421–436 at <http://www.who.int/wer>

## Romidepsin: approved for cutaneous T-cell lymphoma

**United States of America** — The Food and Drug Administration (FDA) has approved romidepsin (Istodax®), an injectable, for treatment of patients with cutaneous T-cell lymphoma (CTCL).

Cutaneous T-cell lymphoma is a slow-growing cancer of T-lymphocytes. Most cases start with dry skin, red rash, and severe itching. The skin may develop tumours that can become ulcerated, causing infection. In some cases, CTCL spreads to the blood, lymph nodes, or internal organs. Patients with localized CTCL on the skin are treated with topical agents or phototherapy, but chemotherapy may be used if the cancer advances. Romidepsin interferes with processes required for cell replication.

Romidepsin evaluation was based on two clinical studies involving 167 patients. About 35% of patients in both of the trials experienced tumour responses which

lasted a median of 15 months in one study and 11 months in the other study. Six per cent of those studied had complete responses, indicating no apparent evidence of the tumour on physical, laboratory, and X-ray examination.

Common side effects include nausea, fatigue, infections, vomiting, decreased appetite, decreased red blood cell count, decreased platelet count, and decreases in the components of white blood cells.

Romidepsin may cause changes in an electrocardiogram (ECG). Periodic blood tests should be carried out to monitor electrolytes, and periodic ECG monitoring should be considered in patients at risk for certain heart rhythm abnormalities. Romidepsin may harm the fetus and women should not become pregnant while taking the drug.

**Reference:** *FDA News Release*, 9 November 2009 at <http://www.fda.gov>

## Orciprenaline sulphate: withdrawal

**United Kingdom** — Orciprenaline sulphate (Alupent®) is to be withdrawn over the next year because a review has concluded that the benefit-risk profile is unfavourable. Patients who require a liquid oral formulation of a  $\beta$ -agonist should be switched to a more-selective short-acting  $\beta_2$ -agonist such as salbutamol or terbutaline

Orciprenaline sulphate (Alupent®) is a non-specific  $\beta$ -agonist indicated for reversible airways obstruction and suggested for maintenance therapy. It is currently available for oral administration as a syrup.

An analysis of the available literature has demonstrated that orciprenaline sulphate is significantly less efficacious than salbutamol in terms of both the extent and duration of bronchodilation. Reports and clinical trial data show a significantly increased incidence of cardiac side effects, mainly palpitations and tachycardia because of its non-selectivity. Importantly, clinical trial data show that cardiac side effects occur before maximum bronchodilation is achieved because of its non-selectivity.

Accordingly, the Commission on Human Medicines (CHM) has advised that the balance of benefit and risks for orciprenaline sulphate is no longer favourable and concluded that:

- There should be a planned withdrawal of orciprenaline sulphate from the UK market.
- There are no patient groups for whom transfer to a more-selective  $\beta_2$ -agonist would be inappropriate.

**Reference:** Medicines and Healthcare Products Regulatory Agency. [http://www.mhra.gov.uk/safety\\_information/](http://www.mhra.gov.uk/safety_information/)

### **Artemisinin antimalarials: not for use as monotherapy**

**Mozambique** — The risks of therapeutic failure and cases of resistance to artemisinin-derived antimalarials are elevated when used as monotherapy. In order to comply with World Health Organization recommendations, the Ministry of Health has determined that circulation in the national market of all artemisinin derived antimalarial medicines for use as monotherapy in oral administration is no longer permitted.

**Reference:** Communication from Ministry of Health, Maputo, Mozambique. Presidential Decree no. 11/95. 4 November 2009

### **Vitespen: withdrawal of marketing authorization application**

**European Union** — The European Medicines Agency (EMA) has been formally notified by the manufacturer of its decision to withdraw an application for a centralized marketing authorization for the medicine vitespen (Oncophage®), 20  $\mu$ g solution for infusion.

Vitespen was expected to be used as an adjuvant treatment for localized renal cell carcinoma patients but received a negative opinion from the Committee for Medicinal Products for Human Use (CHMP) on 19 November 2009.

**Reference:** EMA Press Release, Doc. Ref. EMA/763056/2009, 26 October 2009. <http://www.emea.europa.eu>

### **Aripiprazole: withdrawal of application for extension of indication**

**European Union** — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw an application for an extension of indication for the centrally authorized medicine aripiprazole (Abilify®) tablets, orodispersible tablets and oral solution.

Aripiprazole was expected to be used in the treatment of major depressive episodes, as adjunctive therapy, in patients who have had an inadequate response to previous treatment with antidepressants.

The company stated in its official letter that the withdrawal was based on the CHMP's consideration that the long-term data provided in support of the proposed indication were insufficient, as long-term randomized controlled data are needed before this indication can be licensed.

**Reference:** *EMA Press Release*, Doc. Ref. EMEA/749487/2009 19 November 2009 at <http://www.emea.europa.eu>

## **Substandard and counterfeit medicines: USAID–USP Agreement**

**United States of America** — With substandard and counterfeit versions of medicines intended to treat life-threatening diseases such as malaria, HIV/AIDS and tuberculosis posing a growing threat throughout the developing world, the US Agency for International Development (USAID) and the US Pharmacopeial Convention (USP) have launched a new five-year programme. Promoting the Quality of Medicines (PQM) Programme will serve as a primary mechanism to help assure the quality, safety and efficacy of medicines that are essential to USAID's priority health programmes. This will be achieved by:

- Working with countries to strengthen their medicines regulatory bodies.
- Increasing the supply of good-quality medicines.
- Combating the availability of counterfeit and substandard medicines through testing programmes and other means.
- Conducting global advocacy to raise awareness of the dangers of substandard and counterfeit drugs.

**Reference:** USAID, 26 October 2009 at <http://www.usaid.gov>

## **Vandetinib: withdrawal of marketing authorization application**

**European Union** — The European Medicines Agency (EMA) has been formally notified of the manufacturer's decision to withdraw its application for a centralized marketing authorization for the medicine vandetinib (Zactima®), 100 mg film-coated tablets.

Zactima was expected to be used in combination with chemotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received prior anticancer therapy.

In its official letter, the company stated that the withdrawal of the application was based on preliminary comments which indicate that at this point in time the Committee would be unlikely to conclude on a favourable benefit-risk balance for the product in the treatment of NSCLC in combination with chemotherapy.

**Reference:** *EMA Press Release*, Doc. Ref. EMEA/698692/2009, 30 October 2009 at <http://www.emea.europa.eu>

# Consultation Document

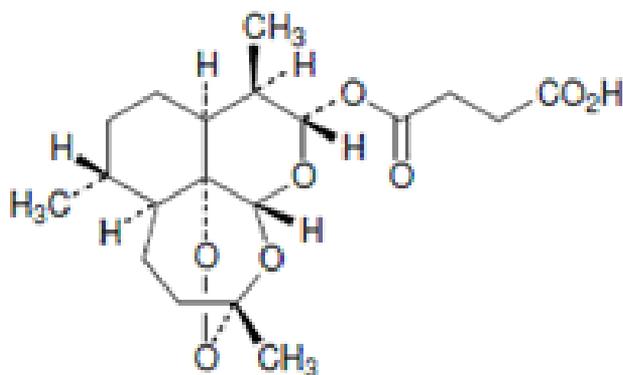
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## The International Pharmacopoeia

### Artesunatum Artesunate

Draft proposal for the *International Pharmacopoeia* (September 2009). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +4122791 4730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

*[Note from Secretariat : The proposed revision deals primarily with the HPLC tests for related substances and assay.]*



*[Note from Secretariat. The structure shows the stereochemistry as corrected for the electronic version of the Ph.Int on the WHO medicines web site.]*

$C_{19}H_{28}O_8$

**Relative molecular mass.** 384.4

**Chemical name.** (3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*pyrano[4,3-*j*]-1,2-benzodioxepin-10-ol, hydrogen succinate; CAS Reg. No. 182824-33-5.

**Description.** A fine, white crystalline powder.

**Solubility.** Very slightly soluble in water; very soluble in dichloromethane R; freely soluble in ethanol (~750 g/l) TS and acetone R.

**Category.** Antimalarial.

**Storage.** Artesunate should be kept in a well-closed container and protected from light.

#### REQUIREMENTS

Artesunate contains not less than 96.0% and not more than the equivalent of 102.0% of artesunate ( $C_{19}H_{28}O_8$ ) using Assay method A, and not less than 99.0% and not more than the equivalent of 101.0% of artesunate ( $C_{19}H_{28}O_8$ ) using Assay method B, both calculated with reference to the anhydrous substance.

#### Identity tests

Either test A alone or tests B, C, and D may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from artesunate RS or with the *reference spectrum* of artesunate.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 5 volumes of ethyl acetate R and 95 volumes of toluene R as the mobile phase. Apply separately to the plate 2  $\mu$ l of the following 2 solutions in toluene R. For solution (A) use 0.10 mg of Artesunate per ml. For solution (B) use 0.10 mg of artesunate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in air, spray with anisaldehyde/methanol TS, and heat the plate to 120 °C for 5 minutes. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. Dissolve 0.1 g of Artesunate in 40 ml of dehydrated ethanol R, shake, and filter. To half of the filtrate (keep the remaining filtrate for test D) add about 0.5 ml of hydroxylamine hydrochloride TS2 and 0.25 ml of sodium hydroxide (~80 g/l) TS. Heat the mixture in a water-bath to boiling, cool, add 2 drops of hydrochloric acid (~70 g/l) TS and 2 drops of ferric chloride (50 g/l) TS; a light red-violet colour is produced.

D. Evaporate the remaining filtrate from test C on a water-bath to a volume of about 5 ml. Place a few drops of the mixture on a white porcelain dish, add 1 drop of vanillin/sulfuric acid TS1; a reddish-brown colour is produced.

*[Note from the Secretariat: melting range test has been deleted.]*

**Specific optical rotation.** Use a 10 mg/ml solution in dichloromethane R and calculate with reference to the anhydrous substance;

$$[\alpha]_D^{20^\circ C} = +4.5^\circ \text{ to } +6.5^\circ.$$

**Heavy metals.** Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 20 µg/g.

**Sulfated ash.** Not more than 1.0 mg/g.

**Water.** Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using 2 g of Artesunate; the water content is not more than 5 mg/g.

**pH value.** pH of an aqueous suspension containing 10 mg/g, 3.5 - 4.5.

### Related substances

*[Note from the Secretariat :*

- *the TLC method has been deleted*
- *HPLC chromatographic system has been changed to allow separation of the β-artenimol peak*
- *limits for related substances have been modified (3 related substances are now specified, and a separate limit for the unknowns is now given)]*

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under Assay method A.

Use solutions (1) and (3) as described under Assay method A. For solution (4) dilute 1 ml of solution (1) to 100 ml with acetonitrile R.

Operate with a flow rate of 1.0 ml per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject separately 20 µl each of solutions (1), (3) and (4). Record the chromatograms for about 4 times the retention time of artesunate. In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to artesunate (retention time about 9 minutes): α-artenimol about 0.58, β-artenimol about 0.91 and impurity B (artemisinin) about 1.30. The assay is not valid unless the resolution factor between the peaks due to β-artenimol and artesunate is at least 1. The chromatogram obtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate.

In the chromatogram obtained with solution (1)

- the combined areas of any peaks corresponding to α-artenimol and β-artenimol (impurity A) are not greater than the area of the principal peak obtained with solution (4) (1.0%);
- the area of any peak corresponding to impurity B (artemisinin) is not greater than 0.5 times the area of the principal peak obtained with solution (4) (0.5%);

- the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.07, is not greater than 0.2 times the area of the principal peak obtained with solution (4) (0.2%);
- the area of any other peak, other than the principal peak, is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);
- The sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than twice the area of the principal peak obtained with solution (4) (2.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

### Assay

Either method A or method B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (10 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (3  $\mu\text{m}$ ) (Luna® has been found suitable). As the mobile phase, use a mixture of 44 volumes of acetonitrile R and 56 volumes of buffer pH 3.0.

Prepare the buffer pH 3.0 by dissolving 1.36 g of potassium dihydrogen phosphate R in 900 ml of water R, adjust the pH to 3.0 with phosphoric acid (~1440 g/l) TS and dilute to 1000 ml with water R.

Prepare the following solutions in acetonitrile R. For solution (1) dissolve 40 mg of the test substance, accurately weighed, and dilute to 10 ml. For solution (2) dissolve 40 mg of artesunate RS, accurately weighed, and dilute to 10 ml. For solution (3) dissolve about 1 mg of artemimol RS, about 1 mg of artemisinin RS and about 10 mg of artesunate RS in 10 ml.

Operate with a flow rate of 1.0 ml per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject separately 20  $\mu\text{l}$  each of solutions (1), (2) and (3). Record the chromatograms for about 4 times the retention time of artesunate. In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to artesunate (retention time about 9 minutes):  $\alpha$ -artemimol about 0.58,  $\beta$ -artemimol about 0.91 and impurity B (artemisinin) about 1.30. The assay is not valid unless the resolution factor between the peaks due to  $\beta$ -artemimol and artesunate is at least 1. The chromatogram obtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate. Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the percentage content of artesunate ( $\text{C}_{19}\text{H}_{28}\text{O}_8$ ) with reference to the anhydrous substance.

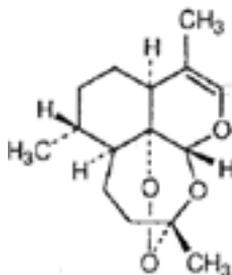
B. Dissolve about 0.25 g of Artesunate, accurately weighed, in 25 ml of neutralized ethanol TS and titrate with sodium hydroxide (0.05 mol/l) VS, using 2 drops of phenolphthalein/ethanol TS as indicator.

Each ml of sodium hydroxide (0.05 mol/l) VS is equivalent to 19.22 mg of  $C_{19}H_{28}O_8$ .

### Impurities

The following list of known and potential impurities that have been shown to be controlled by the tests in this monograph is given for information.

- A. Artenimol
- B. Artemisinin
- C.



(3*R*,5*aS*,6*R*,8*aS*, 12*R*,12*aR*)-Octahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepine; 9,10-Didehydro-10-deoxyartemisinin (Glycan).

*[Note from Secretariat : Systematic name of impurity C to be confirmed.]*

## Artesunati compressi Artesunate tablets

Draft proposal for the *International Pharmacopoeia* (September 2009). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +4122791 4730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

*[Note from Secretariat : The proposed revision deals mainly with the HPLC tests for related substances and assay.]*

**Category.** Antimalarial.

**Storage.** Artesunate tablets should be kept in a well-closed container.

**Additional information.** Strength in the current WHO Model List of Essential Medicines: 50 mg. Strength in the current WHO Model List of Essential Medicines for children: 50 mg.

## REQUIREMENTS

Comply with the monograph for "Tablets".

Artesunate tablets contain not less than 90.0% and not more than 110.0% of the amount of artesunate ( $C_{19}H_{28}O_8$ ) stated on the label.

### Identity tests

Either test A alone or tests B, C, and D may be applied.

A. To a quantity of the powdered tablets containing 0.050 g of Artesunate add 25 ml of acetone R, shake and filter. Evaporate the filtrate at low temperature and dry overnight over desiccant silica gel R. Carry out the examination with the residue as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from artesunate RS or with the *reference spectrum* of artesunate.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 5 volumes of ethyl acetate R and 95 volumes of toluene R as the mobile phase. Apply separately to the plate 2  $\mu$ l of the following 2 solutions in toluene R. For solution (A) shake a quantity of the powdered tablets containing about 0.5 mg of Artesunate with 5 ml, filter and use the clear filtrate. For solution (B) use 0.10 mg of artesunate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in air, spray with anisaldehyde/methanol TS, and heat the plate to 120 °C for 5 minutes. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. To a quantity of the powdered tablets containing 0.1 g of Artesunate add 40 ml of dehydrated ethanol R, shake for a few minutes, and filter. To half of the filtrate (keep the remaining filtrate for test D) add about 0.5 ml of hydroxylamine hydrochloride TS2 and 0.25 ml of sodium hydroxide (~80 g/l) TS. Heat the mixture in a water-bath to boiling, cool, add 2 drops of hydrochloric acid (~70 g/l) TS and 2 drops of ferric chloride (50 g/l) TS; a light red-violet colour is produced.

D. Evaporate the remaining filtrate from test C on a water-bath to a volume of about 5 ml. Place a few drops of the mixture on a white porcelain dish, add 1 drop of vanillin/sulfuric acid TS1, a reddish-brown colour is produced.

### Related substances

*[Note from the Secretariat :*

- *the TLC method has been deleted*
- *HPLC chromatographic system has been changed to allow separation of the  $\beta$ -artenimol peak*
- *limits for related substances have been modified (3 related substances are now specified, and a separate limit for the unknowns is now given).]*

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under Assay method A.

Use solutions (1) and (3) as described below under Assay method A. For solution (4) dilute 1 ml of solution (1) to 100 ml with acetonitrile R. For solution (5) shake or sonicate a mixture of suitable amounts of each of the excipients stated on the label for 15 minutes with 10 ml acetonitrile, filter through a 0.45- $\mu\text{m}$  filter and use the filtrate. Operate with a flow rate of 1.0 ml per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject separately 20  $\mu\text{l}$  each of solutions (1), (3), (4) and (5). Record the chromatograms for about 4 times the retention time of artesunate. In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to artesunate (retention time about 9 minutes):  $\alpha$ -artemimol about 0.58,  $\beta$ -artemimol about 0.91 and impurity B (artemisinin) about 1.30. The assay is not valid unless the resolution factor between the peaks due to  $\beta$ -artemimol and artesunate is at least 1. The chromatogram obtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate.

In the chromatogram obtained with solution (1)

- the combined areas of any peaks corresponding to  $\alpha$ -artemimol and  $\beta$ -artemimol (impurity A) are not greater than 3 times the area of the principal peak obtained with solution (4) (3.0%);
- the area of any peak corresponding to impurity B (artemisinin) is not greater than 0.5 times the area of the principal peak obtained with solution (4) (0.5%);
- the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.07, is not greater than 0.3 times the area of the principal peak obtained with solution (4) (0.3%);
- the area of any other peak, other than the principal peak, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (4) (0.3%);
- the sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than 4 times the area of the principal peak obtained with solution (4) (4.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (4) (0.1%), and any peak eluting before acetonitrile, and, if information concerning the excipients used in manufacturing of the tablets is available, disregard any peak with the same retention time as that of any of the peaks in the chromatogram obtained with solution (5).

### Assay

Either method A or method B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (10 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (3 µm) (Luna® is suitable). As the mobile phase, use a mixture of 44 volumes of acetonitrile R and 56 volumes of buffer pH 3.0.

Prepare the buffer pH 3.0 by dissolving 1.36 g of potassium dihydrogen phosphate R in 900 ml of water R, adjust the pH to 3.0 with phosphoric acid (~1440 g/l) TS and dilute to 1000 ml with water R.

Prepare the following solutions in acetonitrile R. For solution (1) weigh and powder 20 tablets. Shake or sonicate a quantity of the powder containing about 40 mg of Artesunate, accurately weighed, for 15 minutes with 10 ml of acetonitrile R. Filter the resulting solution through a 0.45-µm filter, discarding the first few ml of the filtrate. For solution (2) dissolve 40 mg of artesunate RS, accurately weighed, and dilute to 10 ml. For solution (3) dissolve about 1 mg of arteminol RS, about 1 mg of artemisinin RS and about 10 mg of artesunate RS in 10 ml.

Operate with a flow rate of 1.0 ml per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject separately 20 µl each of solutions (1), (2) and (3). Record the chromatograms for about 4 times the retention time of artesunate. In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to artesunate (retention time about 9 minutes): α-artemamol about 0.58, β-artemamol about 0.91 and impurity B (artemisinin) about 1.30. The assay is not valid unless the resolution factor between the peaks due to β-artemamol and artesunate is at least 1. The chromatogram obtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of artesunate (C<sub>19</sub>H<sub>28</sub>O<sub>8</sub>).

B. Weigh and powder 20 tablets. To a quantity of the powder containing about 0.5 g of Artesunate, accurately weighed, add 50 ml of neutralized ethanol TS, shake thoroughly, filter, and discard about 10 ml of the initial filtrate. Titrate 25 ml of the filtrate with sodium hydroxide (0.05 mol/l) VS, using 2 drops of phenolphthalein/ethanol TS as indicator.

Each ml of sodium hydroxide (0.05 mol/l) VS is equivalent to 19.22 mg of C<sub>19</sub>H<sub>28</sub>O<sub>8</sub>.

**Dissolution.** Analyse the dissolution samples without delay.

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 ml of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 45 minutes withdraw a sample of 10 ml of the medium through an inline filter. Allow the filtered sample to cool to room temperature [solution (1)].

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Determine the concentration in solution (1) by carrying out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5  $\mu\text{m}$ ) (Luna® has been found suitable). As the mobile phase, use a mixture of equal volumes of acetonitrile R and buffer pH 3.0 (prepare the buffer as described under Assay method A).

For solution (2) dissolve 25 mg of artesunate RS, accurately weighed, in acetonitrile R and dilute to 20 ml with the same solvent. Dilute 2 ml of the resulting solution to 50 ml with acetonitrile R.

Operate with a flow rate of 1.5 ml per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at a wavelength of about 210 nm.

Inject alternately 100  $\mu\text{l}$  each of solutions (1) and (2).

For each of the six tablets tested, calculate the total amount of artesunate ( $\text{C}_{19}\text{H}_{28}\text{O}_8$ ) in the medium from the results obtained. The amount in solution for each tablet is not less than 80% of the amount stated on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 75% and the amount obtained for no tablet is less than 60%.

**Impurities.** The impurities limited by the requirements of this monograph include those listed in the monograph for Artesunate.

# Recent Publications, Information and Events

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## Illegal weight-loss medicines and dietary supplements

**Netherlands** — A survey on the health risk of drug substances detected in illegal weight-loss medicines and dietary supplements has recently been published by the National Institute for Public Health and the Environment (RIVM).

Between 2002 and 2007, analyses showed increasing numbers of counterfeit medicines and dietary supplements adulterated with drug substances. Use of these products may lead to psychosis, cardiovascular problems and even death. This is shown by a trend analysis on 256 suspect samples gathered by four national laboratories in the Netherlands, including the RIVM.

Adulterated dietary supplements pose the highest health risks. Because the substances used in the product are not mentioned on the label, consumers are not aware of the risks and assume they are taking a natural product. In the event of an adverse reaction, an adulterated dietary supplement is difficult to identify and correct medical treatment may be delayed.

Health risks are also high for counterfeit medicines because the composition and quality of ingredients are unknown. Internationally, use of illegal weight-loss

medicines and dietary supplements has led to many cases of serious health conditions and occasionally even to death.

**Reference:** Venhuis BJ, Zwaagstra ME, van den Berg JDJ. Trends in drug substances detected in illegal weight-loss medicines and dietary supplements. A 2002-2007 survey and health risk analysis. *RIVM Report*, No. 37003000212009 available at <http://www.rivm.com>

## Southern Med Review

The Southern Med Review (SMR) is a growing independent, open access; peer reviewed journal which is currently published from Auckland, New Zealand. The journal is focusing on pharmaceutical policy and the aim of the journal is to disseminate commentary and empirical research findings, with a view to improve the rational use of and access to essential medicines.

All issues of the journal are freely accessible from the web site and the Editor welcomes submissions for its upcoming issues. Instruction for authors can be downloaded from [http://www.fmhs.auckland.ac.nz/sop/smr/\\_docs/instructiontoauthors.pdf](http://www.fmhs.auckland.ac.nz/sop/smr/_docs/instructiontoauthors.pdf)

**Reference:** University of Auckland at <http://www.fmhs.auckland.ac.nz/sop/smr>