WHO Drug Information

Contents

Announcement

The 13th International Conference of Drug Regulatory Authorities (ICDRA) will be hosted by the Swiss Agency for Therapeutic Products (Swissmedic) in collaboration with the World Health Organization

The ICDRA will take place in Berne, Switzerland from 16 to 19 September 2008

Updated information will be provided regularly at:
http://www.icdra.ch

or

http://www.who.int/medicines/icdra/en/index/html

Safety and Efficacy Issues

Entecavir : not for use in HIV/HBV co–infection

European Union — The Committee for Medicinal Products for Human Use (CHMP) reminds healthcare professionals that entecavir (Baraclude®) has not been evaluated for the treatment of patients with chronic hepatitis B virus (HBV) infection who are co-infected with the human immunodeficiency virus (HIV) and are not receiving highly active antiretroviral therapy (HAART).

Based on new data, the EMEA advises healthcare professionals that:

- Baraclude® has not been evaluated in HIV/HBV co-infected patients not simultaneously receiving effective HIV treatment.
- When considering therapy with entecavir in an HIV/HBV co-infected patient not receiving HAART, there appears to be a risk of developing HIV resistance.
- Until reassuring data become available, Baraclude® should only be considered in this setting under exceptional circumstances.

Reference: European Medicines Agency, Public Statement, EMEA/79902/20075. March 2007.

Deferasirox: acute renal failure and cytopenias

Canada — The manufacturer of deferasirox (Exjade®) has updated the safety information regarding reports of acute renal failure and peripheral blood cytopenias.

Deferasirox is indicated in the management of chronic iron overload in patients with transfusion-dependent anaemias aged 6 years or older. It is also indicated in the management of chronic iron overload in patients with transfusion-dependent anaemias aged two to five who cannot be adequately treated with deferoxamine.

Therapy should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions.

Cases of acute renal failure (some with fatal outcome) have been reported following the post-marketing use of deferasirox. For the fatal cases, it is impossible to completely exclude a contributory role of deferasirox to the renal impairment The fact that there was an improvement after stopping the treatment in most of the cases with non-fatal acute renal failure is suggestive of a contributory role. Deferasirox has not been studied in patients with renal impairment.

Reference: Communication from Novartis Pharmaceuticals Canada Inc. on Medeffect at http://www.hc-sc.gc.ca

Safety of oseltamivir

European Union — The European Medicines Agency (EMEA) has documented new reports of neuropsychiatric adverse events occurring with the use of oseltamivir (Tamiflu®) originating from Japan. These cases have been detected through routine safety monitoring.

The Agency's Committee for Medicinal Products for Human Use (CHMP) has monitored closely all adverse drug reactions reported in connection with the use of oseltamivir since it was introduced in the European Union in 2003.

The CHMP recommended an update of the product information on neuropsychiatric side effects: "Convulsion, depressed level of consciousness, abnormal behaviour, hallucinations and delirium have been reported during Tamiflu® administration, leading in rare cases to accidental injury. Patients, especially children and adolescents should be closely monitored and their healthcare professional should be contacted immediately if the patient shows any signs of unusual behaviour."

The EMEA and CHMP will continue to closely monitor any emerging safety information on Tamiflu®, including neuropsychiatric disorders. If any concerns emerge, further action will be taken. With these measures in place, the CHMP maintains its opinion that the benefits of Tamiflu® outweigh its risks when the product is used according to the adopted recommendations.

Reference: *EMEA Press Release,* 23 March 2007. Doc. Ref. EMEA/134566/2007. http://www.emea.europa.eu

Fluticasone: reports of behavioural changes

Netherlands — The Netherlands Pharmacovigilance Centre, Lareb, has received 17 reports of behavioural changes in children associated with the use of inhaled fluticasone propionate or salmeterol/fluticasone propionate (4). In 11 cases, symptoms disappeared when fluticasone propionate was withdrawn. A positive rechallenge was observed in one case. Six patients who had received fluticasone propionate also received salbutamol. However, in all but one case, the reporter did not see a causal relationship between the adverse drug reaction and salbutamol. Psychiatric effects have also been reported in association with the use of oral corticosteroids and inhaled budesonide, which raises the possibility of a group effect.

Reference: Fluticasone inhalation and behavioural changes in children. Lareb, Netherlands Pharmacovigilance Centre, January 2007 (www.lareb.nl).

Quetiapine: pancreatitis and thrombocytopenia

Canada — Quetiapine (Seroquel®) is an atypical antipsychotic drug indicated for the management of symptoms of schizophrenia and the acute management of manic episodes associated with bipolar disorder (1). In Canada, quetiapine has been marketed since December 1997.

From 1997 to 2006, Health Canada has received 615 domestic reports of adverse reactions suspected of being associated with the use of quetiapine. Nine reports involved cases of pancreatitis and 11 involved cases of thrombocytopenia. Neither of these ARs is mentioned in the Canadian product monograph (1).

Pancreatitis

The 9 reported cases of pancreatitis involved patients aged 24–71 years. In 5 cases, quetiapine was the only suspect drug; in the other cases, reported co-suspect drugs included medications that have been associated with pancreatitis: clozapine, divalproex sodium, fenofibrate and minocycline (2, 3).

Acute pancreatitis typically presents as an acute inflammation of the pancreas that may or may not involve the surrounding tissues (2). Gallstones and heavy alcohol use are the most common causes (2). The severity of drug-induced pancreatitis is variable; the majority of pa-

tients recover without any long-term morbidity, but 5% –15% of patients experience life-threatening complications (4). People at risk of drug-induced pancreatitis include elderly patients taking multiple medications, patients who are HIV positive, patients who have cancer and patients receiving immunomodulatory agents (5).

Thrombocytopenia
The 11 reported cases of thrombocytopenia involved patients aged 28–84 years. In 6 cases, quetiapine was the only suspect drug. In 5 cases, reported co-suspect drugs included medications that have been associated with thrombocytopenia: citalopram, clozapine, olanzapine, pantoprazole, rofecoxib and zuclopenthixol (6–12).

Thrombocytopenia is usually defined as a platelet count of less than 150 x 109/L or a 50% decrease in the platelet count from baseline (6). Some reports define drug-induced thrombocytopenia as a platelet count of less than 100 x 109/L (6). Although relatively rare, drug-induced thrombocytopenia may be associated with risks of morbidity and mortality (6). Perhaps because of its low incidence and idiosyncratic nature, drug-induced thrombocytopenia has often gone unrecognized during early clinical trials of drugs and was first reported after marketing (6).

Extracted from Canadian Adverse Reaction Newsletter, Volume 17, Number 2, 2007

References

1. Seroquel (quetiapine fumarate tablets) [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2006.

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5. Adverse Drug Reactions Advisory Committee (ADRAC). Drug induced pancreatitis. *Aust Adv Drug Reactions Bull,* 2006;**25**(6):22.

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7. Kentos A, Robin V, Lambermont M, et al. Probable rofecoxib-induced thrombocytopenia. *Rheumatology,* 2003;**42**(5):699–700.

8. Hirshberg B, Gural A, Caraco Y. Zuclopenthixol-associated neutropenia and thrombocytopenia. *Ann Pharmacother,* 2000;**34**(6): 740–2.

9. Huynh M, Chee K, Lau DH. Thrombotic thrombocytopenic purpura associated with quetiapine. *Ann Pharmacother,* 2005;**39**(7–8):1346-8.

10. Watson TD, Stark JE, Vesta KS. Pantoprazole-induced thrombocytopenia. *Ann Pharmacother,* 2006;**40**(4):758–61.

11. Celexa (citalopram hydrobromide tablets) [product monograph]. Montreal: Lundbeck Canada Inc.; 2006.

12. Clozaril (clozapine tablets) [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2006.

Aprotinin: hypersensitivity reactions and renal dysfunction

Canada — Health Canada has informed hospitals and pharmacies of an association of aprotinin (Trasylol®) with hypersensitivity reactions and renal dysfunction. Aprotinin is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in

those patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft (CABG) surgery who are at increased risk for blood loss and blood transfusion requirement.

The authorized indication for Trasylol® is restricted to those patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft (CABG) surgery who are at increased risk for blood loss and blood transfusion.

Trasylol® administration may cause fatal and nonfatal anaphylactic or anaphylactoid reactions. Fatal reactions have occurred with an initial (test) dose as well as with any of the components of the dose regimen. Fatal reactions have also occurred in situations where the initial (test) dose was tolerated. As a result, Trasylol® should only be administered in operative settings where cardiopulmonary bypass can be rapidly initiated.

The risk for anaphylactic or anaphylactoid reactions is increased among patients with prior aprotinin exposure, and a history of any prior aprotinin exposure must be sought prior to Trasylol® administration. The risk for a fatal reaction appears to be greater upon re-exposure. As a result, administration of Trasylol® to patients with a known or suspected previous aprotinin exposure during the last 12 months is contraindicated.

Trasylol® administration increases the risk of renal dysfunction and may increase the need for dialysis in the perioperative period. This risk may be especially increased for patients with pre-existing renal impairment or those who receive aminoglycoside antibiotics or drugs that alter renal function.

Reference: Information Update 2007-36, 31 March 2007: Communication from Bayer Inc. on http://.www.hc-sc.gc.ca

Metoclopramide in children: extrapyramidal symptoms

Netherlands — Following an increase in the number of registered cases of extrapyramidal symptoms in children receiving metoclopramide, the Medicines Evaluation Board has restricted the use of metoclopramide in this population to treatment of severe nausea and vomiting of known origin, and only if treatment with other products is ineffective or is not possible.

The MEB considers there are better alternatives to metoclopramide. For example, domperidone is a better choice in treating post-operative nausea in children. Domperidone is also the drug of choice in treating migraine in children because the risk of extrapyramidal effects is lower than with metoclopramide. Similarly, 5-HT3 receptor antagonists (e.g. ondansetron) are the drugs of choice in nausea due to strongly emetogenic chemotherapy because of better efficacy and fewer adverse events.

Reference: News and Publications. The Medicines Evaluation Board, the Netherlands, 21 February 2007. http://www.cbg-meb.nl/uk/nieuws

Drug–eluting stents: to be used with caution

Sweden — The Swedish Medical Products Agency (MPA), in conjunction with the National Board of Health and Welfare and the Swedish Society of Cardiology, has recommended utmost restraint in the use of drug-eluting stents. The recommendation was based on the results of clinical studies, including the Swedish Coronary and Angioplasty Registry (SCAAR) study that showed increased risk of thrombosis associated with the use of drug-eluting stents. The results of the SCAAR study and four other randomized studies showed that drug-eluting stents

have no advantages in terms of myocardial infarction or mortality, compared with bare-metal stents; in addition, the SCAAR study data indicated a small, long-term increased risk of these events. According to the MPA, drug-eluting stents must only be used in patients for whom no other treatment alternative exists or in patients who are at greatly increased risk of restenosis and for whom the effect of restenosis is expected to be severe.

Reference: Swedish Medical Products Agency, 13 February 2007. http://www.lakemedelsverket.se.

Darbepoetin alfa and epoetin alfa: update for non–myeloid malignancies

Canada — The manufacturers of the erythropoiesis-stimulating agents (ESAs), have updated safety information based on completed or ongoing clinical studies regarding treatment with darbepoetin alfa (Aranesp®) and epoetin alfa (Eprex®).

Darbepoetin alfa is indicated for the treatment of anaemia associated with chronic renal failure, and for the treatment of anaemia in patients with non-myeloid malignancies, where anaemia is due to the effect of concomitantly administered chemotherapy.

Epoetin alfa (Eprex®) is indicated for the treatment of anaemia associated with chronic renal failure, the treatment of anaemia in patients with non-myeloid malignancies, where anaemia is due to the effect of concomitantly administered chemotherapy, the treatment of anaemia in zidovudine-treated/HIV-infected patients, and for the treatment of patients undergoing major elective surgery to facilitate autologous blood collection, and to reduce allogeneic blood exposure.

Epoetin alfa is no longer indicated in the treatment of anaemia in patients with non-myeloid malignancies, where anaemia is due to the disease itself. Therefore, none of the ESAs are indicated in this patient population. Recent clinical studies have provided new safety information regarding the use of ESAs, including risks of tumour progression and serious cardiovascular events.

ESAs increased the risk of death and of serious cardiovascular adverse events in patients with cancer or renal failure, when treated to a target haemoglobin level of greater than 120 g/L.

An increased risk of death was seen in cancer patients with active malignant disease, who were not being treated with either radiation or chemotherapy and who were treated with ESAs to a target haemoglobin level of 120 g/L. ESAs are not indicated in this patient population.

ESAs shortened the time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy; in addition, ESAs decreased overall survival and increased deaths at 4 months, attributed to disease progression in patients with metastatic breast cancer receiving chemotherapy, when these groups of patients were treated to a target haemoglobin level of greater than 120 g/L.

Reference: Communication from Amgen Canada, Inc. 16 April 2007 on http://www.hc-sc.gc.ca

Ayurvedic and Chinese medicines: heavy metals

Australia — The Therapeutic Goods Administration (TGA) has released a statement about the safety of Ayurvedic medicines in Australia, in response to recent research into the toxic content of heavy metals found in some Ayurvedic medicines (1).

There are several possible explanations for the presence of heavy metals in traditional herbal remedies (2). Salts of

heavy metals (for example those of lead, mercury and arsenic) are used as principal ingredients in some traditional Indian and (to a lesser extent) Chinese herbal remedies (4). In addition, cross-contamination of ingredients can occur between these types of products and products not intended to contain metal salts if manufacturing conditions are not controlled.

The possibility of contamination and adulteration should be considered for any herb or herbal medicine purchased overseas or imported for personal use, or obtained over the internet.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 26, Number 1, 2007

References

1. Safety of Ayurvedic medicine in Australia. www.tga.gov.au/cm/ayurvedic.htm

2. Ernst E. Contamination of herbal medicines. *The Pharmaceutical Journal* 2005; **275**; 167

3. Pharmacopoeia of the People's Republic of China. Beijing, China: People's Medical Publishing House 2005.

ADHD drugs: cardiovascular and psychiatric events

United States of America — The Food and Drug Administration (FDA) has directed the manufacturers of all drug products approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) to develop Patient Medication Guides concerning risks of possible cardiovascular and psychiatric events.

An FDA review of reports of serious cardiovascular adverse events in patients taking usual doses of ADHD products revealed reports of sudden death in patients with underlying serious heart problems or defects, and reports of stroke and heart attack in adults with certain risk factors.

Another FDA review of ADHD medicines revealed a slight increased risk (about 1 per 1000) for drug-related psychiatric adverse events, such as hearing voices, becoming suspicious for no reason, or becoming manic, even in patients who did not have previous psychiatric problems.

The medicines that are the focus of the revised labelling and new Patient Medication Guides include the following:

Adderall® (mixed salts of a single entity amphetamine product) Tablets

Adderall® XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules

Concerta® (methylphenidate hydrochloride) Extended-Release Tablets

Daytrana® (methylphenidate) Transdermal System

Desoxyn® (methamphetamine HCl) Tablets

Dexedrine® (dextroamphetamine sulfate)

Spansule® Capsules and Tablets

Focalin® (dexmethylphenidate hydrochloride) Tablets

Focalin® XR (dexmethylphenidate hydrochloride) Extended-Release Capsules

Metadate® CD (methylphenidate hydrochloride) Extended-Release Capsules

Methylin® (methylphenidate hydrochloride) Oral Solution

Methylin® (methylphenidate hydrochloride) Chewable Tablets

Ritalin® (methylphenidate hydrochloride) Tablets

Ritalin® SR (methylphenidate hydrochloride) Sustained-Release Tablets

Ritalin® LA (methylphenidate hydrochloride) Extended-Release Capsules

Strattera® (atomoxetine HCl) Capsules

Reference: *FDA News,* P07-26, 21 February 2007 with draft Patient Medication Guides for each product at http://www.fda.gov/cder/drug/infopage/ADHD/default.htm.

Clozapine can impair motility of the entire GI tract

New Zealand — Clozapine (Clozaril®, Clopine®) is an atypical antipsychotic that is effective for treatment-resistant schizophrenia. It causes agranulocytosis in up to 1% of patients (1) and regular monitoring of neutrophil counts is mandatory throughout treatment. In New Zealand one death from agranulocytosis has been reported. In contrast, four deaths from complications of severe constipation have been reported to the Intensive Medicines Monitoring Programme. Health professionals are reminded that the gastrointestinal (GI) effects of clozapine are potentially serious.

Constipation is often regarded as a frequent, minor side effect of clozapine. However, review of New Zealand reports shows that clozapine-induced constipation may be associated with serious effects such as intestinal obstruction, bowel perforation and toxic megacolon.

In addition to reports of constipation associated with clozapine, there have been three reports of paralytic ileus and a further three reports of oesophageal dysmotility. These case reports suggest that clozapine may reduce GI motility throughout the gut, resulting in complications higher in the GI tract.

Many anticholinergic drugs can cause GI dysmotility, but clozapine has a much more potent effect through its interaction with multiple receptors (including anticholinergic and serotonergic receptors) affecting GI activity. This action is exacerbated by co-prescription of anticholinergic agents such as benztropine and tricyclic antidepressants.

References

1. Alvir JMJ, Lieberman JA, Safferman AZ, et al. Clozapine-induced agranulocytosis. *New England Journal of Medicine* 1993;**329**:162-167

2. PM Ellis. Clozapine: Fatal 'constipation' more common than fatal agranulocytosis. *Prescriber Update*. March 2007. http://www.medsafe.govt.nz

Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.

Essential Medicines

15th Model List of Essential Medicines

Model List updated
The WHO Model List of Essential Medicines allows countries to select medicines of public health priority, address problems of cost and availability and provides guidance to pharmaceutical manufacturers on medicine needs.

During its 2007 meeting in Geneva, the WHO Expert Committee on Essential Medicines made a number of important updates to the Model List of Essential Medicines (set out on the following pages). These included the addition of five fixed-dose-combinations to treat HIV/AIDS in adults, two of which are available in generic form, and antimalarials recommended by WHO.

Five oral liquid formulations were included for children — three for epilepsy, one for children born prematurely, and one new medicine for HIV/AIDS. Three other epilepsy medicines were included in the form of chewable, dispersable tablets which are also effective in children.

A medicines list for children
Following recommendations from the Expert Committee, work will begin to create a list if essential medicines specifically tailored to children's needs. A group of experts will meet in July 2007 to begin work on a list of medicines to address diseases of high mortality and morbidity in children.

Children suffer from the same illnesses as adults but they are more seriously affected by certain conditions such as respiratory tract infections, malaria and diarrhoeal diseases — particularly in developing countries. An estimated 10.6 million children under five die every year, many from treatable conditions. In 2005, 2.3 million children under 15 years were HIV positive.

In spite of the huge need, there are few formulations appropriate for children or that can be easily consumed by a child. At present, children must often take crushed adult tablets, with little evidence to guide the efficacy and safety of the dose. When medicines do exist in the right dosage they are usually in syrup form, which may pose supply, storage and pricing problems in developing countries.

The challenge for children becomes more acute when they are affected by a condition requiring combination therapy, such as HIV/AIDS and malaria. In these cases, fixed dose combination tablets are required. While production of adult fixed-dose-combinations is increasing, these are lacking for children. In addition, antiretrovirals for children are currently three times more expensive than the adult versions.

WHO will also work with partners to advocate innovation and research into children's medicines, manufacture of new dosage forms and new formulas, and mechanisms to relay information about children's medicines to countries quickly and effectively.

Reference: *WHO News Release*. WHO/17. 13 April 2007 http://www.who.int

WHO Model List of Essential Medicines

15th Edition, revised March 2007

Explanatory Notes

The **core list** presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

The **square box symbol (■)** is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price. Medicines are listed in alphabetical order, within sections.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of each local regulatory authority to ensure that each brand is of appropriate pharmaceutical quality (including stability) and that, when relevant, different brands are interchangeable.

Dosage forms of medicines are listed in alphabetical order and there is no implication of preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

Entries of the type *oral liquid* are intended to permit any solution, suspension or other form of liquid. Granules for reconstitution as an oral liquid may substitute for oral liquids, and typically carry benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar, and that solutions for children do not contain alcohol.

Entries of the type *tablet* are intended to allow various forms of immediate-release tablet such as uncoated, film-coated, crushable, chewable, dispersible etc. Enteric coating, on the other hand, modifies drug release, and enteric-coated products are a modified release dosage form. Crushable, chewable and dispersible tablets may be easier to administer to paediatric populations and to the elderly.

1. Anaesthetics

1.1 General anaesthetics and oxygen

■ halothane	inhalation
ketamine	injection: 50 mg (as hydrochloride)/ml in 10-ml vial
nitrous oxide	inhalation
oxygen	inhalation (medicinal gas)
■ thiopental	powder for injection: 0.5 g, 1.0 g (sodium salt) in ampoule

1.2 Local anaesthetics

■ bupivacaine	Injection: 0.25%; 0.5% (hydrochloride) in via.
	Injection for spinal anaesthesia: 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution
■ lidocaine	Injection: 1%; 2% (hydrochloride) in vial
	Injection for spinal anaesthesia: 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution
	Topical forms: 2–4% (hydrochloride)
lidocaine + epinephrine (adrenaline)	Dental cartridge: 2% (hydrochloride) + epinephrine 1:80 000
	Injection: 1%; 2% (hydrochloride) + epinephrine 1:200 000 in vial

Complementary List

ephedrine	*Injection: 30 mg (hydrochloride)/ml in 1-ml ampoule (For use in spinal anaesthesia during delivery, to prevent hypotension)*

1.3 Preoperative medication and sedation for short-term procedures

atropine	Injection: 1 mg (sulfate) in 1-ml ampoule
■ diazepam	Injection: 5 mg/ml in 2-ml ampoule
	Tablet: 5 mg
morphine	Injection: 10 mg (sulfate or hydrochloride) in 1-ml ampoule
promethazine	Oral liquid: 5 mg (hydrochloride)/5 ml

2. Analgesics, antipyretics, non-steroidal anti-inflammatory medicines (NSAIMs), medicines used to treat gout and disease modifying agents in rheumatoid disorders (DMARDs)

2.1 Nonopioids and nonsteroidal anti-inflammatory medicines (NSAIMs)

acetylsalicylic acid	Suppository: 50–150 mg
	Tablet: 100–500 mg
ibuprofen	Tablet: 200 mg; 400 mg
paracetamol*	Oral liquid: 125 mg/5 m
	Suppository: 100 mg
	Tablet: 100–500 mg

** Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.*

2.2 Opioid analgesics

codeine	Tablet: 30 mg (phosphate)
morphine	Injection: 10 mg (morphine hydrochloride or morphine sulfate) in 1-ml ampoule
	Oral liquid: 10 mg (morphine hydrochloride or morphine sulfate)/5 ml
	Tablet: 10 mg (morphine sulfate)
	Tablet (prolonged release): 10 mg; 30 mg; 60 mg (morphine sulfate)

2.3 Medicines used to treat gout

allopurinol	Tablet: 100 mg

2.4 Disease modifying agents used in rheumatoid disorders (DMARDs)

chloroquine	Tablet: 100 mg; 150 mg (as phosphate or sulfate).

Complementary List

azathioprine	*Tablet: 50 mg*
methotrexate	*Tablet: 2.5 mg (as sodium salt)*
penicillamine	*Capsule or tablet: 250 mg*
sulfasalazine	*Tablet: 500 mg*

3. Antiallergics and medicines used in anaphylaxis

■ chlorphenamine	Injection: 10 mg (hydrogen maleate) in 1-ml ampoule
	Tablet: 4 mg (hydrogen maleate)
dexamethasone	Injection: 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule
epinephrine (adrenaline)	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
hydrocortisone	Powder for injection: 100 mg (as sodium succinate) in vial
■ prednisolone*	Tablet: 5 mg; 25 mg

** There is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.*

4. Antidotes and other substancess used in poisonings

4.1 Non-specific

charcoal, activated	Powder

4.2 Specific

acetylcysteine	Injection: 200 mg/ml in 10-ml ampoule
atropine	Injection: 1 mg (sulfate) in 1-ml ampoule
calcium gluconate	Injection: 100 mg/ml in 10-ml ampoule
deferoxamine	Powder for injection: 500 mg (mesilate) in vial
dimercaprol	Injection in oil: 50 mg/ml in 2-ml ampoule
DL-methionine	Tablet: 250 mg
methylthioninium chloride (methylene blue)	Injection: 10 mg/ml in 10-ml ampoule
naloxone	Injection: 400 micrograms (hydrochloride) in 1-ml ampoule
penicillamine	Capsule or tablet: 250 mg
potassium ferric hexacyanoferrate(II) -2$H_2$0 (Prussian blue)	Powder for oral administration
sodium calcium edetate	Injection: 200 mg/ml in 5-ml ampoule
sodium nitrite	Injection: 30 mg/ml in 10-ml ampoule
sodium thiosulfate	Injection: 250 mg/ml in 50-ml ampoule

5. Anticonvulsants/antiepileptics

carbamazepine	Oral liquid: 100 mg/5 ml
	Tablet (chewable): 100 mg; 200 mg
	Tablet (scored): 100 mg; 200 mg
■ diazepam	Injection: 5 mg/ml in 2-ml ampoule (intravenous or rectal)
magnesium sulfate*	Injection: 500 mg/ml in 2-ml ampoule; 500 mg/ml in 10-ml ampoule

** For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.*

phenobarbital	Injection: 200 mg/ml (phenobarbital sodium)
	Oral liquid: 15 mg/5 ml (phenobarbital) or 5 ml (phenobarbital sodium)
	Tablet: 15-100 mg (phenobarbital)
phenytoin	Capsule: 25 mg; 50 mg; 100 mg (sodium salt)
	Injection: 50 mg/ml in 5-ml vial (sodium salt)
	Oral liquid: 25-30 mg/5 ml.*
	Tablet: 25 mg; 50 mg; 100 mg (sodium salt)
	Tablet (chewable): 50 mg

** The presence of both 25 mg/5 ml and 30 mg/5 ml strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.*

valproic acid	Oral liquid: 200 mg/5 ml
	Tablet (crushable): 100 mg
	Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate)

Complementary List

ethosuximide	*Capsule: 250 mg*
	Oral liquid: 250 mg/5 ml

6. Anti-infective medicines

6.1 Anthelminthics

6.1.1 Intestinal anthelminthics

albendazole — Tablet (chewable): 400 mg

levamisole — Tablet: 50 mg; 150 mg (as hydrochloride)

■ mebendazole — Tablet (chewable): 100 mg; 500 mg

niclosamide* — Tablet (chewable): 500 mg

** Niclosamide is listed for use when praziquantel treatment fails.*

praziquantel — Tablet: 150 mg; 600 mg

pyrantel — Oral liquid: 50 mg (as embonate)/ml

Tablet (chewable): 250 mg (as embonate)

6.1.2 Antifilarials

ivermectin — Tablet (scored): 3 mg; 6 mg

Complementary List

diethylcarbamazine — *Tablet: 50 mg; 100 mg (dihydrogen citrate)*

suramin sodium — *Powder for injection: 1 g in vial*

6.1.3 Antischistosomals and antitrematode medicine

praziquantel — Tablet: 600 mg

triclabendazole — Tablet: 250 mg

Complementary List

oxamniquine* — Capsule: 250 mg

Oral liquid: 250 mg/5 ml

** Oxamniquine is listed for use when praziquantel treatment fails.*

6.2 Antibacterials

6.2.1 Beta Lactam medicines

amoxicillin — Capsule or tablet: 250 mg; 500 mg (anhydrous)

Powder for oral liquid: 125 mg (anhydrous)/5 ml

amoxicillin + clavulanic acid — Tablet: 500 mg + 125 mg

ampicillin — Powder for injection: 500 mg; 1 g (as sodium salt) in vial

benzathine benzylpenicillin — Powder for injection: 1.44 g benzylpenicillin (=2.4 million IU) in 5-ml vial

benzylpenicillin — Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial

cefazolin* — Powder for injection: 1 g (as sodium salt) in vial

** For surgical prophylaxis.*

cefixime* — Capsule: 400 mg

** Only listed for single-dose treatment of uncomplicated ano-genital gonorrhoea.*

■ cloxacillin — Powder for injection: 500 mg (as sodium salt) in vial

Capsule: 500 mg; 1 g (as sodium salt)

Powder for oral liquid: 125 mg (as sodium salt)/5 ml

phenoxymethylpenicillin — Powder for oral liquid: 250 mg (as potassium salt)/5 ml

Tablet: 250 mg (as potassium salt)

procaine benzylpenicillin — Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial

Complementary List

ceftazidime — *Powder for injection: 250 mg (as pentahydrate) in vial*

■ *ceftriaxone* — *Powder for injection: 250 mg, 1 g (as sodium salt) in vial*

imipenem + cilastatin ** — *Powder for injection: 250 mg (as monohydrate) + 250 mg (as sodium salt); 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial*

** Only listed for the treatment of life-threatening hospital-based infection due to suspected or proven multidrug-resistant infection.*

6.2.2 Other antibacterials

azithromycin* — Capsule: 250 mg or 500 mg

Oral liquid: 200 mg/5 ml

** Only listed for single-dose treatment of genital Chlamydia trachomatis and of trachoma.*

chloramphenicol	Capsule: 250 mg
	Oily suspension for injection: 0.5 g (as sodium succinate)/ml in 2-ml ampoule
	Oral liquid: 150 mg (as palmitate)/5 ml
	Powder for injection: 1 g (sodium succinate) in vial
■ ciprofloxacin*	Tablet: 250 mg (as hydrochloride)
** Final selection depends on indication for use.*	
doxycycline*	Capsule or tablet: 100 mg (hydrochloride)
** Final selection depends on indication for use.*	
■ erythromycin	Capsule or tablet: 250 mg (as stearate or ethyl succinate)
	Powder for injection: 500 mg (as lactobionate) in vial
	Powder for oral liquid: 125 mg (as stearate or ethyl succinate)
■ gentamicin*	Injection: 10 mg; 40 mg (as sulfate)/ml in 2-ml vial
** Final selection depends on indication for use.*	
■ metronidazole	Injection: 500 mg in 100-ml vial
	Oral liquid: 200 mg (as benzoate)/5 ml
	Suppository: 500 mg; 1 g
	Tablet: 200-500 mg
nitrofurantoin	Tablet: 100 mg
spectinomycin	Powder for injection: 2 g (as hydrochloride) in vial
sulfamethoxazole + trimethoprim	Injection: 80 mg + 16 mg/ml in 5-ml and 10-ml ampoules
	Oral liquid: 200 mg + 40 mg/5 ml
	Tablet: 100 mg + 20 mg; 400 mg + 80 mg
trimethoprim	Tablet: 100 mg; 200 mg

Complementary List

clindamycin	*Capsule: 150 mg*
	Injection: 150 mg (as phosphate)/ml
sulfadiazine	*Injection: 250 mg (sodium salt) in 4-ml ampoule*
	Tablet: 500 mg
vancomycin	*Powder for injection: 250 mg (as hydrochloride) in vial*

6.2.3 Antileprosy medicines

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour coded blister packs (MDT blister packs) containing standard two medicine (paucibacillary leprosy) or three medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

clofazimine	Capsule: 50 mg; 100 mg
dapsone	Tablet: 25 mg; 50 mg; 100 mg
rifampicin	Capsule or tablet: 150 mg; 300 mg

6.2.4 Antituberculosis medicines

ethambutol	Tablet: 100–400 mg (hydrochloride)
isoniazid	Tablet: 100–300 mg
	Tablet (scored): 50 mg
isoniazid + ethambutol	Tablet: 150 mg + 400 mg
pyrazinamide	Tablet: 400 mg
	Tablet (dispersible): 150 mg
	Tablet (scored): 150 mg
rifampicin	Capsule or tablet: 150 mg; 300 mg
rifampicin + isoniazid	Tablet: 60 mg + 30 mg; 150 mg + 75 mg; 300 mg + 150 mg
	60 mg + 60 mg (For intermittent use three times weekly)
	150 mg + 150 mg (For intermittent use three times weekly)
rifampicin + isoniazid + ethambutol	Tablet: 150 mg + 75 mg + 275 mg
rifampicin + isoniazid + pyrazinamide	Tablet: 60 mg + 30 mg + 150 mg; 150 mg + 75 mg + 400 mg
	150 mg + 150 mg + 500 mg (For intermittent use three times weekly)
rifampicin + isoniazid + pyrazinamide + ethambutol	Tablet: 150 mg + 75 mg + 400 mg + 275 mg

streptomycin — Powder for injection: 1 g (as sulfate) in vial

Complementary List

Reserve second-line drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.

amikacin — *Powder for injection: 1000 mg in vial*

ρ-aminosalicylic acid — *Granules: 4 g in sachet*

Tablet: 500 mg

capreomycin — *Powder for injection: 1000 mg in vial*

cycloserine — *Capsule or tablet: 250 mg*

ethionamide — *Tablet: 125 mg; 250 mg*

kanamycin — *Powder for injection: 1000 mg in vial*

*ofloxacin** — *Tablet: 200 mg; 400 mg*

** Levofloxacin may be an alternative based on availability and programme considerations.*

6.3 Antifungal medicines

clotrimazole — Vaginal cream: 1%; 10%

Vaginal tablet: 100 mg; 500 mg

■ fluconazole — Capsule: 50 mg

Injection: 2 mg/ml in vial

Oral liquid: 50 mg/5 ml

griseofulvin — Capsule or tablet: 125 mg; 250 mg

nystatin — Lozenge: 100 000 IU

Pessary: 100 000 IU

Tablet: 100 000 IU; 500 000 IU

Complementary List

amphotericin B — *Powder for injection: 50 mg in vial*

flucytosine — *Capsule: 250 mg*

Infusion: 2.5 g in 250 ml

potassium iodide — *Saturated solution*

6.4 Antiviral medicines

6.4.1 Antiherpes medicines

■ aciclovir — Powder for injection: 250 mg (as sodium salt) in vial

Tablet: 200 mg

6.4.2 Antiretrovirals

Based on current evidence and experience of use, medicines in the following three classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post exposure prophylaxis). The Committee emphasizes the importance of using these products in accordance with global and national guidelines. The Committee recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms with assured pharmaceutical quality.

6.4.2.1 Nucleoside/nucleotide reverse transcriptase inhibitors

abacavir (ABC) — Oral liquid: 100 mg (as sulfate)/5 m

Tablet: 300 mg (as sulfate)

didanosine (ddI) — Buffered powder for oral liquid: 100 mg; 167 mg; 250 mg packets

Capsule (unbuffered enteric-coated): 125 mg; 200 mg; 250 mg; 400 mg

Tablet (buffered chewable, dispersible): 25 mg; 50 mg; 100 mg; 150 mg; 200 mg

emtricitabine (FTC)* — Capsule: 200 mg

Oral liquid: 10 mg/ml

** 3TC is an acceptable alternative to FTC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.*

lamivudine (3TC) — Tablet: 150 mg

Oral liquid: 50 mg/5 ml

stavudine (d4T) — Capsule: 15 mg; 20 mg; 30 mg; 40 mg*

** The Committee expects this dosage form to be reviewed for possible deletion at the next meeting.*

Powder for oral liquid: 5 mg/5 ml

tenofovir — Capsule: 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)

zidovudine — Capsule: 100 mg; 250 mg

(ZDV or AZT) — Oral liquid: 50 mg/5 ml

Solution for IV infusion injection: 10 mg/ml in 20-ml vial

Tablet: 300 mg

6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

efavirenz (EFV or EFZ) — Capsule: 50 mg; 100 mg; 200 mg

Oral liquid: 150 mg/5 ml

Tablet: 600 mg

nevirapine (NVP) — Oral liquid: 50 mg/5 ml

Tablet: 200 mg

6.4.2.3 Protease inhibitors

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right.

This section will be reviewed by the Committee as a priority at its next meeting. It is expected that application for a heat stable tablet formulation containing 200/50 mg lopinavir + ritonavir will be submitted for the next meeting.

indinavir (IDV) — Capsule: 200 mg; 333 mg; 400 mg (as sulfate).

lopinavir + ritonavir (LPV/r) — Capsule: 133.3 mg + 33.3 mg

Oral liquid: 400 mg + 100 mg/5 ml

nelfinavir (NFV) — Oral powder: 50 mg/g

Tablet: 250 mg (as mesilate)

ritonavir — Oral liquid: 400 mg/5 ml

Oral solid dosage form: 100 mg

saquinavir (SQV) — Capsule: 200 mg

FIXED-DOSE COMBINATIONS

efavirenz + emtricitabine* + tenofovir — Tablet: 600 mg + 200 mg + 300 mg

** 3TC is an acceptable alternative to FTC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.*

emtricitabine* + tenofovir — Tablet: 200 mg + 300 mg

** 3TC is an acceptable alternative to FTC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.*

stavudine + lamivudine + nevirapine — Tablet: 30 mg + 150 mg + 200 mg

zidovudine + lamivudine — Tablet: 300 mg + 150 mg

zidovudine + lamivudine + nevirapine — Tablet: 300 mg + 150 mg + 200 mg

6.4.3 Other antivirals

ribavirin — Injection for intravenous administration: 1000 mg and 800 mg in 10-ml phosphate buffer solution

Oral solid dosage forms: 200 mg; 400 mg; 600 mg

6.5 Antiprotozoal medicines

6.5.1 Antiamoebic and antigiardiasis medicines

diloxanide — Tablet: 500 mg (furoate)

■ metronidazole — Injection: 500 mg in 100-ml vial

Oral liquid: 200 mg (as benzoate)/5 ml

Tablet: 200-500 mg

6.5.2 Antileishmaniasis medicines

■ meglumine antimoniate — Injection, 30%, equivalent to approximately 8.1% antimony in 5-ml ampoule

paromomycin — Solution for intramuscular injection: 750 mg/2 ml (as sulfate)

Complementary List

amphotericin B — *Powder for injection: 50 mg in vial*

pentamidine — *Powder for injection: 200 mg; 300 mg (isetionate) in vial*

6.5.3 Antimalarial medicines

6.5.3.1 For curative treatment

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. The Committee recognizes that not all of these FDCs exist and encourages their development and rigorous testing. The Committee also encourages development and testing of rectal dosage formulations.

amodiaquine* — Tablet: 153 mg or 200 mg (as hydrochloride)

** To be used (a) in combination with artesunate 50 mg OR (b) may be used alone for the treatment of* Plasmodium vivax, P.ovale *and* P.malariae *infections.*

artemether — Oily injection: 80 mg/ml in 1-ml ampoule

For use in the management of severe malaria.

artemether + lumefantrine* — Tablet: 20 mg + 120 mg

** Not recommended in the first trimester of pregnancy or in children below 5 kg.*

artesunate* — Injection: ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution

For use in the management of severe malaria.

Tablet: 50 mg

** To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.*

chloroquine — Oral liquid: 50 mg (as phosphate or sulfate)/5 ml

Tablet: 100 mg; 150 mg (as phosphate or sulfate)

doxycycline* — Capsule: 100 mg (as hydrochloride)

Tablet (dispersible): 100 mg (as monohydrate)

** For use only in combination with quinine.*

mefloquine* — Tablet: 250 mg (as hydrochloride)

** To be used in combination with artesunate 50 mg*

primaquine* — Tablet: 7.5 mg; 15 mg (as diphosphate)

** Only for use to achieve radical cure of* P.vivax *and* P.ovale *infections, given for 14 days.*

quinine* — Injection: 300 mg quinine hydrochloride/ml in 2-ml ampoule

Tablet: 300 mg (quinine sulfate) or 300 mg (quinine bisulfate)

** For use only in the management of severe malaria, and should be used in combination with doxycycline.*

sulfadoxine + * pyrimethamine — Tablet: 500 mg + 25 mg

** Only in combination with artesunate 50 mg*

6.5.3.2 For prophylaxis

chloroquine* — Oral liquid: 50 mg (as phosphate or sulfate)/5 ml

Tablet: 150 mg (as phosphate or sulfate)

** For use only in central American regions for* P.vivax.

doxycycline — Capsule or tablet: 100 mg (hydrochloride)

mefloquine — Tablet: 250 mg (as hydrochloride)

proguanil* — Tablet: 100 mg (hydrochloride)

** For use only in combination with chloroquine.*

6.5.4 Antipneumocystosis and antitoxoplasmosis medicines

pyrimethamine — Tablet: 25 mg

sulfamethoxazole + trimethoprim — Injection: 80 mg + 16 mg/ml in 5-ml ampoule; 80 mg + 16 mg/ml in 10-ml ampoule

Complementary List

pentamidine — *Tablet: 200 mg; 300 mg*

6.5.5 Antitrypanosomal medicines

6.5.5.1 African trypanosomiasis

Medicines for the treatment of 1st stage African trypanosomiasis

pentamidine* — Powder for injection: 200 mg (pentamidine isetionate) in vial

** To be used for the treatment of* Trypansoma brucei gambiense *infection.*

suramin sodium* — Powder for injection: 1 g in vial.

** To be used exclusively for the treatment of the initial phase of* T. brucei rhodesiense *infection.*

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine — Injection: 200 mg (hydrochloride)/ml in 100-ml bottle

melarsoprol — Injection: 3.6% solution, 5-ml ampoules (180 mg of active compound)

6.5.5.2 American trypanosomiasis

benznidazole — Tablet: 100 mg

nifurtimox — Tablet: 30 mg; 120 mg; 250 mg

7. Antimigraine medicines

7.1 For treatment of acute attack

acetylsalicylic acid — Tablet: 300-500 mg

paracetamol — Tablet: 300-500 mg

7.2 For prophylaxis

■ propranolol — Tablet: 20 mg; 40 mg (hydrochloride)

8. Antineoplastic, immuno-suppressives and medicines used in palliative care

8.1 Immunosuppressive medicines

Complementary List

azathioprine	*Powder for injection: 100 mg (as sodium salt) in vial*
	Tablet: 50 mg
ciclosporin	*Capsule: 25 mg*
	Concentrate for injection: 50 mg/ml in 1-ml ampoule for organ transplantation

8.2 Cytotoxic medicines

This section is expected to be reviewed at the next meeting.

Complementary List

asparaginase	*Powder for injection: 10 000 IU in vial*
bleomycin	*Powder for injection: 15 mg (as sulfate) in vial*
calcium folinate	*Injection: 3 mg/ml in 10-ml ampoule*
	Tablet: 15 mg
chlorambucil	*Tablet: 2 mg*
cisplatin	*Powder for injection: 10 mg; 50 mg in vial*
cyclophosphamide	*Powder for injection: 500 mg in vial*
	Tablet: 25 mg
cytarabine	*Powder for injection: 100 mg in vial*
dacarbazine	*Powder for injection: 100 mg in vial*
dactinomycin	*Powder for injection: 500 micrograms in vial*
daunorubicin	*Powder for injection: 50 mg (as hydrochloride)*
doxorubicin	*Powder for injection: 10 mg; 50 mg (hydrochloride) in vial*
etoposide	*Capsule: 100 mg*
	Injection: 20 mg/ml in 5-ml ampoule
fluorouracil	*Injection: 50 mg/ml in 5-ml ampoule*
mercaptopurine	*Tablet: 50 mg*
methotrexate	*Powder for injection: 50 mg (as sodium salt) in vial*
	Tablet: 2.5 mg (as sodium salt)
procarbazine	*Capsule: 50 mg (as hydrochloride)*
vinblastine	*Powder for injection: 10 mg (sulfate) in vial*
vincristine	*Powder for injection: 1 mg; 5 mg (sulfate) in vial*

8.3 Hormones and antihormones

Complementary List

dexamethasone	*Injection: 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule*
hydrocortisone	*Powder for injection: 100 mg (as sodium succinate) in vial*
■ *prednisolone**	*Tablet: 5 mg; 25 mg*

** There is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.*

tamoxifen	*Tablet: 10 mg; 20 mg (as citrate)*

8.4 Medicines used in palliative care

The WHO Expert Committee recognizes the importance of listing specific medicines in the Palliative Care Section. Some medicines currently used in palliative care are included in the relevant sections of the Model List, according to their therapeutic use, e.g. analgesics. The Guidelines for Palliative Care that were referenced in the previous list are in need of update. The Committee expects applications for medicines needed for palliative care to be submitted for the next meeting.

9. Antiparkinsonism medicines

biperiden	Injection: 5 mg (lactate) in 1-ml ampoule
	Tablet: 2 mg (hydrochloride)
levodopa + ■ carbidopa	Tablet: 100 mg + 10 mg; 250 mg + 25 mg

10. Medicinces affecting the blood

10.1 Antianaemia medicines

ferrous salt	Oral liquid: equivalent to 25 mg iron (as sulfate)/ml

	Tablet: equivalent to 60 mg iron
ferrous salt + folic acid (Nutritional supplement for use during pregnancy)	Tablet equivalent to 60 mg iron + 400 micrograms folic acid
folic acid	Tablet: 1 mg; 5 mg
hydroxocobalamin	Injection: 1 mg in 1-ml ampoule

10.2 Medicines affecting coagulation

heparin sodium	Injection: 1000 IU/ml; 5000 IU/ml; 20,000 IU/ml in 1-ml ampoule
phytomenadione	Injection: 10 mg/ml in 5-ml ampoule
	Tablet: 10 mg
protamine sulfate	Injection: 10 mg/ml in 5-ml ampoule
■ warfarin	Tablet: 1 mg; 2 mg; 5 mg (sodium salt)

11. Blood products and plasma substitutes

11.1 Plasma substitutes

■ dextran 70*	Injectable solution: 6%

* Polygeline, injectable solution, 3.5% is considered as equivalent

11.2 Plasma fractions for specific use

All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). (WHO Technical Report Series, No. 840, 1994, Annex 2).

Complementary List

human normal immunoglobulin	*Intravenous administration: 5%, 10% protein solution*
	Intramuscular administration: 16% protein solution
■ *factor VIII concentrate*	*Dried*
■ *factor IX complex (coagulation factors, II, VII, IX, X) concentrate*	*Dried*

12. Cardiovascular medicines

12.1 Antianginal medicines

■ atenolol	Tablet: 50 mg; 100 mg
glyceryl trinitrate	Tablet (sublingual): 500 micrograms
■ isosorbide dinitrate	Tablet (sublingual): 5 mg
verapamil	Tablet: 40 mg; 80 mg (hydrochloride)

12.2 Antiarrhythmic medicines

This subsection will be reviewed at the next meeting of the Expert Committee.

■ atenolol	Tablet: 50 mg; 100 mg
digoxin	Injection: 250 micrograms/ml in 2-ml ampoule
	Oral liquid: 50 micrograms/ml
	Tablet: 62.5 micrograms; 250 micrograms
epinephrine (adrenaline)	Injection: 100 micrograms/ml (as acid tartrate or hydrochloride) in 10-ml ampoule
lidocaine	Injection: 20 mg (hydrochloride)/ml in 5-ml ampoule
verapamil	Injection: 2.5 mg (hydrochloride)/ml in 2-ml ampoule
	Tablet: 40 mg; 80 mg (hydrochloride)

Complementary List

■ *procainamide*	*Injection: 100 mg (hydrochloride)/ml in 10-ml ampoule.*
■ *quinidine*	*Tablet: 200 mg (sulfate)*

12.3 Antihypertensive medicines

■ amlodipine	Tablet: 5 mg
■ atenolol	Tablet: 50 mg; 100 mg
■ enalapril	Tablet: 2.5 mg
hydralazine*	Powder for injection: 20 mg (hydrochloride) in ampoule
	Tablet: 25 mg, 50 mg (hydrochloride)

* Hydralazine is listed for use in the acute management of severe pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.

■ hydrochlorothiazide	Tablet (scored): 25 mg
methyldopa*	Tablet: 250 mg

* Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the

treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.

Complementary List

sodium nitroprusside	*Powder for infusion: 50 mg in ampoule*

12.4 Medicines used in heart failure

This subsection will be reviewed at the next meeting of the Expert Committee.

digoxin	Injection: 250 micrograms/ml in 2-ml ampoule
	Oral liquid: 50 micrograms/ml
	Tablet: 62.5 micrograms; 250 micrograms
■ enalapril	Tablet: 2.5 mg
■ furosemide	Injection: 10 mg/ml in 2-ml ampoule
	Tablet: 40 mg
■ hydrochlorothiazide	Tablet (scored): 25 mg

Complementary List

dopamine	*Injection: 40 mg (hydrochloride) in 5-ml vial*

12.5 Antithrombotic medicines

acetylsalicylic acid	Tablet: 100 mg

Complementary List

streptokinase	*Powder for injection: 1.5 million IU in vial*

12.6 Lipid-lowering agents

■ simvastatin*	Tablet: 5 mg; 10 mg; 20 mg; 40 mg

* For use in high-risk patients.

13. Dermatological medicines (topical)

13.1 Antifungal medicines

benzoic acid + salicylic acid	Ointment or cream: 6% + 3%
■ miconazole	Ointment or cream: 2% (nitrate)
sodium thiosulfate	Solution: 15%

Complementary List

selenium sulfide	*Detergent-based suspension: 2%*

13.2 Anti-infective medicines

■ methylrosanilinium chloride (gentian violet)	Aqueous solution: 0.5%
	Tincture: 0.5%
neomycin sulfate + ■ bacitracin	Ointment: 5 mg neomycin sulfate + 250 IU bacitracin zinc/g
potassium permanganate	Aqueous solution: 1:10 000
silver sulfadiazine	Cream: 1%, in 500-g container

13.3 Anti-inflammatory and antipruritic medicines

■ betamethasone	Ointment or cream: 0.1% (as valerate)
■ calamine lotion	Lotion
■ hydrocortisone	Ointment or cream: 1% (acetate)

13.4 Astringent medicines

aluminium diacetate	Solution: 5%

13.5 Medicines affecting skin differentiation and proliferation

benzoyl peroxide	Lotion or cream: 5%
coal tar	Solution: 5%
dithranol	Ointment: 0.1%-2%
fluorouracil	Ointment: 5%
■ podophyllum resin	Solution: 10-25%
salicylic acid	Solution: 5%
urea	Ointment or cream: 10%

13.6 Scabicides and pediculicides

■ benzyl benzoate	Lotion: 25%
permethrin	Cream: 5%
	Lotion: 1%

14. Diagnostic agents

14.1 Ophthalmic medicines

fluorescein	Eye drops: 1% (sodium salt)

■ tropicamide	Eye drops: 0.5%

14.2 Radiocontrast media

■ amidotrizoate	Injection: 140-420 mg iodine (as sodium or meglumine salt)/ ml in 20-ml ampoule
barium sulfate	Aqueous suspension
■ iohexol	Injection: 140-350 mg iodine/ ml in 5-ml; 10-ml; 20-ml ampoule

Complementary List

■ *meglumine iotroxate*	*Solution: 5-8 g iodine in 100-250 ml*

15. Disinfectants and antiseptics

15.1 Antiseptics

■ chlorhexidine	Solution: 5% (digluconate) for dilution
■ ethanol	Solution: 70% (denatured)
■ polyvidone iodine	Solution: 10%

15.2 Disinfectants

■ chlorine base compound	Powder: (0.1% available chlorine) for solution
■ chloroxylenol	Solution: 4.8%
glutaral	Solution: 2%

16. Diuretics

amiloride	Tablet: 5 mg (hydrochloride)
■ furosemide	Injection: 10 mg/ml in 2-ml ampoule
	Tablet: 40 mg
■ hydrochlorothiazide	Tablet (scored): 25 mg
mannitol	Injectable solution: 10%; 20%
spironolactone	Tablet: 25 mg

17. Gastrointestinal medicines

17.1 Antacids and other antiulcer medicines

aluminium hydroxide	Oral liquid: 320 mg/5 ml
	Tablet: 500 mg
■ ranitidine	Injection: 25 mg/ml in 2-ml ampoule
	Oral liquid: 75 mg/5 ml
	Tablet: 150 mg (as hydrochloride)
magnesium hydroxide	Oral liquid: equivalent to 550 mg magnesium oxide/10 ml

17.2 Antiemetic medicines

metoclopramide	Injection: 5 mg (hydrochloride)/ ml in 2-ml ampoule
	Tablet: 10 mg (hydrochloride)
promethazine	Injection: 25 mg (hydrochloride)/ ml in 2-ml ampoule
	Oral liquid: 5 mg (hydrochloride)/5 ml
	Tablet: 10 mg; 25 mg (hydrochloride)

17.3 Anti-inflammatory medicines

■ sulfasalazine	Retention enema
	Suppository: 500 mg
	Tablet: 500 mg

Complementary List

■ *hydrocortisone*	*Retention enema*
	Suppository: 25 mg (acetate)

(■ only applies to hydrocortisone retention enema).

17.4 Laxatives

■ senna	Tablet: 7.5 mg (sennosides) (or traditional dosage forms)

17.5 Medicines used in diarrhoea

17.5.1 Oral rehydration

oral rehydration salts*

glucose:	75 mEq
sodium:	75 mEq or mmol/l
chloride:	65 mEq or mmol/l
potassium:	20 mEq or mmol/l
citrate:	10 mmol/l
osmolarity:	245 mOsm/l
glucose:	13.5 g/l
sodium chloride:	2.6 g/l
potassium chloride:	1.5 g/l
trisodium citrate dihydrate+:	2.9 g/l

+ trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/l. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use.

** In cases of cholera, a higher concentration of sodium may be required.*

17.5.2 Medicines for diarrhoea in children

zinc sulfate*	Oral liquid: in 10 mg per unit dosage forms
	Tablet: in 10 mg per unit dosage forms

* In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.

17.5.3 Antidiarrhoeal (symptomatic) medicines in adults

codeine*	Tablet: 30 mg (phosphate)

* The role of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

18. Hormones, other endocrine medicines and contraceptives

18.1 Adrenal hormones and synthetic substitutes

Addison's disease is a rare condition; adrenal hormones are already included in section 3.

18.2 Androgens

Complementary List

testosterone	*Injection: 200 mg (enantate) in 1-ml ampoule*

18.3 Contraceptives

18.3.1 Oral hormonal contraceptives

■ ethinylestradiol + ■ levonorgestrel	Tablet: 30 micrograms + 150 micrograms
■ ethinylestradiol + ■ norethisterone	Tablet: 35 micrograms + 1.0 mg
levonorgestrel	Tablet: 30 micrograms; 750 micrograms (pack of two); 1.5 mg

18.3.2 Injectable hormonal contraceptives

medroxyprogesterone acetate	Depot injection: 150 mg/ml in 1-ml vial
medroxyprogesterone acetate + estradiol cypionate	Injection: 25 mg + 5 mg
norethisterone enantate	Oily solution: 200 mg/ml in 1-ml ampoule

18.3.3 Intrauterine devices

copper-containing device

18.3.4 Barrier methods

condoms

diaphragms

18.3.5 Implantable contraceptives

levonorgestrel-releasing implant	Two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg total)

18.4 Estrogens

■ ethinylestradiol*	Tablet: 10 micrograms; 50 micrograms

* The public health relevance and/or comparative efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

18.5 Insulins and other antidiabetic agents

glibenclamide	Tablet: 2.5 mg; 5 mg
insulin injection (soluble)	Injection: 40 IU/ml in 10-ml vial; 100 IU/ml in 10-ml vial
intermediate-acting insulin	Injection: 40 IU/ml in 10-ml vial; 100 IU/ml in 10-ml vial (as compound insulin zinc suspension or isophane insulin)
metformin	Tablet: 500 mg (hydrochloride)

18.6 Ovulation inducers

Complementary List

clomifene	*Tablet: 50 mg (citrate)*

18.7 Progestogens

norethisterone*	Tablet: 5 mg

* The public health relevance and/or comparative efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

Complementary List

*medroxyprogesterone acetate**	*Tablet: 5 mg*

** The public health relevance and/or comparative efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.*

18.8 Thyroid hormones and antithyroid medicines

levothyroxine	Tablet: 50 micrograms; 100 micrograms (sodium salt)
potassium iodide	Tablet: 60 mg
■ propylthiouracil	Tablet: 50 mg

19. Immunologicals

19.1 Diagnostic agents

All tuberculins should comply with the WHO Requirements for Tuberculins (Revised 1985). WHO Expert Committee on Biological Standardization. Thirty-sixth report. (WHO Technical Report Series, No. 745, 1987, Annex 1).

tuberculin, purified protein derivative (PPD)	Injection

19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). WHO Expert Committee on Biological Standardization. Forty-third report. (WHO Technical Report Series, No. 840, 1994, Annex 2).

anti-D immunoglobulin (human)	Injection: 250 micrograms in single-dose vial
antitetanus immunoglobulin (human)	Injection: 500 IU in vial
antivenom immunoglobulin*	Injection

* Exact type to be defined locally.

diphtheria antitoxin	Injection: 10 000 IU; 20 000 IU in vial
■ rabies immunoglobulin	Injection: 150 IU/ml in vial

19.3 Vaccines

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities. The list below details the vaccines for which there is either a recommendation from the Strategic Advisory Group of Experts on Immunization (SAGE) (http://www.who.int/immunization/sage_conclusions/en/index.html) and/or a WHO position paper (http://www.who.int/immunization/documents/positionpapers/en/index.html). This site will be updated as new position papers are published and contains the most recent information and recommendations.

All vaccines should comply with the WHO Requirements for Biological Substances.

BCG vaccine

cholera vaccine

diphtheria vaccine

hepatitis A vaccine

hepatitis B vaccine

Haemophilus influenzae type b vaccine

influenza vaccine

Japanese encephalitis vaccine

measles vaccine

meningococcal meningitis vaccine

mumps vaccine

pertussis vaccine

pneumococcal vaccine

poliomyelitis vaccine

rabies vaccine

rotavirus vaccine

rubella vaccine

tetanus vaccine

typhoid vaccine

varicella vaccine

yellow fever vaccine

20. Muscle relaxants (peripherally acting) and cholinesterase inhibitors

■ alcuronium	Injection: 5 mg (chloride)/ml in 2-ml ampoule
neostigmine	Injection: 500 micrograms in 1-ml ampoule; 2.5 mg (metilsulfate) in 1-ml ampoule
	Tablet: 15 mg (bromide)
suxamethonium	Injection: 50 mg (chloride)/ml in 2-ml ampoule
	Powder for injection (chloride), in vial

Complementary List

pyridostigmine	*Injection: 1 mg in 1-ml ampoule*

Tablet: 60 mg (bromide)

■ *vecuronium* — *Powder for injection: 10 mg (bromide) in vial*

21. Ophthalmological preparations

This section will be reviewed at the next meeting of the Expert Committee.

21.1 Anti-infective agents

aciclovir — Ointment: 3% W/W

■ gentamicin* — Solution (eye drops): 0.3% (sulfate)

* Final selection depends on indication for use.

■ tetracycline — Eye ointment: 1% (hydrochloride)

21.2 Anti-inflammatory agents

■ prednisolone — Solution (eye drops): 0.5% (sodium phosphate)

21.3 Local anaesthetics

■ tetracaine — Solution (eye drops): 0.5% (hydrochloride)

21.4 Miotics and antiglaucoma medicines

acetazolamide — Tablet: 250 mg

■ pilocarpine — Solution (eye drops): 2%; 4% (hydrochloride or nitrate)

■ timolol — Solution (eye drops): 0.25%; 0.5% (as maleate)

21.5 Mydriatics

atropine — Solution (eye drops): 0.1%; 0.5%, 1% (sulfate)

Complementary List

epinephrine (adrenaline) — *Solution (eye drops): 2% (as hydrochloride)*

22. Oxytocics and antioxytocics

22.1 Oxytocics

■ ergometrine — Injection: 200 micrograms (hydrogen maleate) in 1-ml ampoule

oxytocin — Injection: 10 IU in 1-ml ampoule

Complementary List

misoprostol — *Vaginal tablet: 25 micrograms*

mifepristone – misoprostol** — *Tablet 200 mg – tablet 200 micrograms*

** Requires close medical supervision.*

Where permitted under national law and where culturally acceptable.

22.2 Antioxytocics (tocolytics)

nifedipine — Immediate release capsule: 10 mg

23. Peritoneal dialysis solution

Complementary List

intraperitoneal dialysis solution (of appropriate composition) — *Parenteral solution*

24. Psychotherapeutic medicines

24.1 Medicines used in psychotic disorders

■ chlorpromazine — Injection: 25 mg (hydro chloride)/ml in 2-ml ampoule

Oral liquid: 25 mg (hydrochloride)/5 ml

Tablet: 100 mg (hydrochloride)

■ fluphenazine — Injection: 25 mg (decanoate or enantate) in 1-ml ampoule

■ haloperidol — Injection: 5 mg in 1-ml ampoule

Tablet: 2 mg; 5 mg

24.2 Medicines used in mood disorders

24.2.1 Medicines used in depressive disorders

■ amitriptyline — Tablet: 25 mg (hydrochloride)

fluoxetine — Capsule or tablet: 20 mg (present as hydrochloride)

24.2.2 Medicines used in bipolar disorders

carbamazepine — Tablet (scored): 100 mg; 200 mg

lithium carbonate — Capsule or tablet: 300 mg

valproic acid — Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate)

24.3 Medicines used in generalized anxiety and sleep disorders

■ diazepam — Tablet (scored): 2 mg; 5 mg

24.4 Medicines used for obsessive compulsive disorders and panic attacks

clomipramine	Capsule: 10 mg; 25 mg (hydrochloride)

24.5 Medicines used in substance dependence programmes

Complementary List

■ *methadone**	*Concentrate for oral liquid: 5 mg/ml; 10 mg/ml (hydrochloride)*
	Oral liquid: 5 mg/5 ml; 10 mg/5 ml

** The square box is added to include buprenorphine. The medicines should only be used within an established support programme.*

25. Medicines acting on the respiratory tract

25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease

■ beclometasone	Inhalation (aerosol): 50 micrograms per dose (dipropionate); 250 micrograms (dipropionate) per dose
epinephrine (adrenaline)	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
ipratropium bromide	Inhalation (aerosol): 20 micrograms/metered dose
■ salbutamol	Inhalation (aerosol): 100 micrograms (as sulfate) per dose
	Injection: 50 micrograms (as sulfate)/ml in 5-ml ampoule
	Oral liquid: 2 mg/5 ml
	Respirator solution for use in nebulizers: 5 mg (as sulfate)/ml
	Tablet: 2 mg; 4 mg (as sulfate)

25.2 Other medicines acting on the respiratory tract

caffeine citrate	Injection: 20 mg/ml (equivalent to 10 mg caffeine base/ml)
	Oral liquid: 20 mg/ml (equivalent to 10 mg caffeine base/ml)

26. Solutions correcting water, electrolyte and acid–base disturbances

26.1 Oral

oral rehydration salts	See section 17.5.1
potassium chloride	Powder for solution

26.2 Parenteral

glucose	Injectable solution: 5%; 10% isotonic; 50% hypertonic
glucose with sodium chloride	Injectable solution: 4% glucose, 0.18% sodium chloride (equivalent to Na^+ 30 mmol/l, Cl- 30 mmol/l)
potassium chloride	Solution: 11.2% in 20-ml ampoule (equivalent to K^+ 1.5 mmol/ml, Cl^- 1.5 mmol/ml)
sodium chloride	Injectable solution: 0.9% isotonic (equivalent to Na^+ 154 mmol/l, Cl- 154 mmol/l
sodium hydrogen carbonate	Injectable solution: 1.4% isotonic (equivalent to Na^+ 167 mmol/l, HCO_3- 167 mmol/l)
	Solution: 8.4% in 10-ml ampoule (equivalent to Na^+ 1000 mmol/l, HCO_3-1000 mmol/l)
■ sodium lactate, compound solution	Injectable solution

26.3 Miscellaneous

water for injection	2-ml; 5-ml; 10-ml ampoules

27. Vitamins and minerals

ascorbic acid	Tablet: 50 mg
■ ergocalciferol	Capsule or tablet: 1.25 mg (50 000 IU)
	Oral liquid: 250 micrograms/ml (10 000 IU/ml)
iodine	Capsule: 200 mg
	Iodized oil: 1 ml (480 mg iodine); 0.5 ml (240 mg iodine) in ampoule (oral or injectable); 0.57 ml (308 mg iodine) in dispenser bottle

■ nicotinamide	Tablet: 50 mg
pyridoxine	Tablet: 25 mg (hydrochloride)
retinol	Capsule: 50 000 IU; 100 000 IU; 200 000 IU (as palmitate)
	Oral oily solution: 100 000 IU (as palmitate)/ml in multidose dispenser
	Tablet (sugar-coated): 10 000 IU (as palmitate)
	Water-miscible injection: 100 000 IU (as palmitate) in 2-ml ampoule
riboflavin	Tablet: 5 mg
sodium fluoride	In any appropriate topical formulation
thiamine	Tablet: 50 mg (hydrochloride)

Complementary List

calcium gluconate	*Injection: 100 mg/ml in 10-ml ampoule*

Regulatory Action and News

Tegaserod: marketing suspension

Canada — Marketing and sales of tegaserod hydrogen maleate (Zelnorm®) tablets have been suspended in Canada to permit further evaluation of important safety information.

Zelnorm® is a serotonin 5-HT4 receptor partial agonist indicated for the symptomatic treatment of irritable bowel syndrome with constipation in female patients whose main symptoms are constipation and abdominal pain and/or discomfort and for the treatment of chronic idiopathic constipation in patients under 65 years of age.

A recent retrospective analysis of pooled clinical trial data showed that the incidence of cardiovascular ischemic events (1) in patients taking Zelnorm® was higher than in those taking placebo:

Canadian pharmacists and distributors have been requested to return the product to the company. Patients should discontinue treatment and contact their physician for advice about alternative therapies.

Reference: Communication from Novartis Pharmaceuticals Canada Inc. 30 March 2007 posted by Medeffect at http://www.hc-sc.gc.ca

United States of America — The Food and Drug Administration (FDA) has informed patients and health care professionals that tegaserod maleate (Zelnorm®) will no longer be marketed. A new safety analysis has found a higher chance of heart attack, stroke, and worsening heart chest pain in patients treated with tegaserod compared to placebo. Zelnorm® is a prescription medication approved for short term treatment of women with irritable bowel syndrome with constipation and for patients younger than 65 years with chronic constipation.

Patients should contact their physician to discuss alternative treatments for their condition. Physicians should work with their patients and transition them to other therapies as appropriate to their symptoms and need.

Thirteen patients treated with Zelnorm® (0.1%) had serious and life-threatening cardiovascular side effects; among these, four patients had a heart attack (one died), six had a type of severe heart chest pain which can quickly turn into a heart attack, and three had a stroke.

The FDA has indicated a willingness to consider limited re-introduction of Zelnorm® at a later date if a population of patients can be identified in whom the benefits of the drug outweigh the risks. However, before FDA makes a decision about limited re-introduction, any proposed plan would be discussed at a public advisory committee meeting.

Reference: FDA Public Health Advisory, 30 March 2007

Pergolide: voluntary withdrawal of products

United States of America — The Food and Drug Administration (FDA) has announced that manufacturers of pergolide drug products, used to treat Parkinson disease, will voluntarily remove these drugs from the market because of the risk of serious damage to patients' heart valves. The products being with-

drawn are Permax®, the trade name for pergolide, and two generic versions

Two new studies showed that patients with Parkinson disease who were treated with pergolide had an increased chance of serious damage to their heart valves when compared to patients who did not receive the drug. Pergolide is a dopamine agonist used with levodopa and carbidopa to manage the signs and symptoms of Parkinson disease.

Healthcare professionals who prescribe pergolide should consider the following:

- If continued treatment is necessary, another dopamine agonist should be substituted for pergolide. There are other dopamine agonists approved for the treatment of Parkinson disease that are not associated with heart valve damage. Published transition regimens describe the conversion from one DA to another.

- If treatment with a dopamine agonist is to be discontinued, pergolide should not be stopped abruptly, because rapid discontinuation of all dopamine agonist therapies can be dangerous. Instead, gradually decrease the dose of pergolide.

- Patients who will be taken off pergolide should be told that other effective options for treatment exist, including three other dopamine agonists that are not associated with damage to heart valves.

One of the drugs included in the recent studies showing increased chance of heart valve problems is cabergoline (Dostinex®), another dopamine agonist. This drug is approved in the US for the treatment of hyperproteinaemia disorders. Dostinex® is not approved in the US for the treatment of Parkinson disease. For hyperproteinaemia disorders, a considerably lower dose of Dostinex® is used.

Reference: *FDA News,* P07-54 and *Public Health Advisory*, 29 March 2007 at http://www.fda.gov

Aliskiren approved for hypertension

United States of America — The Food and Drug Administration (FDA) has announced the approval of aliskiren (Tekturna®) tablets for the treatment of hypertension. Aliskiren acts by inhibiting renin.

Effectiveness was demonstrated in six placebo-controlled eight-week clinical trials, which studied over 2000 patients with mild to moderate hypertension. The effect was maintained for up to one year. When used in combination with hydrochlorothiazide, further reductions in blood pressure were achieved.

Aliskiren was effective across all demographic subgroups, but African American patients tended to have smaller reductions in blood pressure than Caucasians and Asians, as is generally true for drugs that affect the renin-angiotensin system.

Side effects were usually mild and brief. Diarrhoea was reported by approximately 2 percent of patients on the higher of the two approved doses, compared with approximately 1 percent on placebo. Rarely, patients developed an allergic reaction with swelling of the face, lips or tongue and difficulty breathing. This has been seen with other drugs for high blood pressure that act directly on the renin-angiotensin system.

Aliskiren and other drugs that act directly on the renin-angiotensin system should not be used during pregnancy.

Reference: *FDA News*, P07-38. 6 March 2007 at http://www.fda.gov

Lapatinib approved for advanced breast cancer

United States of America —The Food and Drug Administration (FDA) has approved lapatinib (Tykerb ®), a targeted anti-cancer treatment to be used in combination with capectabine (Xeloda®) for patients with advanced, metastatic breast cancer that is HER2 positive. The combination treatment is indicated for women who have received prior therapy with other cancer drugs, including an anthracycline, a taxane, and trastuzumab. According to the American Cancer Society, about 180 000 new cases of breast cancer are diagnosed each year.

Lapatinib is a kinase inhibitor unlike, for example, trastuzumab — a monoclonal antibody, which is a large protein molecule that targets the part of the HER2 protein on the outside of the cell. Because of this difference in mechanism of action, Tykerb® works in some HER2 positive breast cancers that are no longer benefiting from trastuzumab.

Commonly reported side effects included diarrhoea, nausea, vomiting, rash and hand-foot syndrome which may include numbness, tingling, redness, swelling and discomfort of hands and feet. Generally reversible decreases in heart function have also been reported in a small percentage of patients.

Reference: *FDA News,* P07-44, 13 March 2007 at http://www.fda.gov

Adalimumab approved for Crohn disease

United States of America — The Food and Drug Administration (FDA) has approved adalimumab (Humira®) to treat adult patients with moderate to severe Crohn disease. Adalimumab is a human-derived, genetically-engineered monoclonal antibody to reduce excessive levels of human tumour necrosis factor alpha, which plays an important role in abnormal inflammatory and immune responses. The labelling includes a boxed warning about potential serious adverse events. Adalimumab has been studied in 1478 patients with Crohn disease in four clinical trials comparing the drug to a placebo and two longer term extension studies.

Use of this product has been associated with serious, sometimes fatal, infections, including cases of tuberculosis, opportunistic infections, and sepsis. Before initiating adalimumab treatment, patients should be evaluated for tuberculosis risk factors and tested for latent tuberculosis infection. Other serious adverse events reported by adalimumab users include lymphoma. The most frequent adverse events included upper respiratory infections, sinusitis, and nausea.

Humira® was previously approved for the treatment of three autoimmune diseases: rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

Reference: *FDA News*, P07-30. 27 February 2007 at http://www.fda.gov

Rapid test for meningitis cleared for marketing

United States of America — The Food and Drug Administration (FDA) has cleared for marketing a test that uses molecular biology to quickly detect the presence of viral meningitis.

The Xpert EV® test, when used in combination with other laboratory tests, will help physicians distinguish between viral and bacterial meningitis.

Meningitis is diagnosed by testing the fluid obtained from a patient during a spinal tap. Typically, diagnostic tests for meningitis can take up to a week to get

results. But results from the Xpert EV test are available in two and one-half hours.

The accuracy of the Xpert EV® test was confirmed in a multi-site study at six institutions. A total of 255 patient samples were tested and demonstrated that 96 percent of patients who tested positive did have viral meningitis, and that 97 percent of patients who tested negative did not have viral meningitis.

Reference: *FDA News;* P07-46, 16 March 2007 at http://www.fda.gov

Eculizumab approved for paroxysmal nocturnal haemoglobinuria

United States of America —The Food and Drug Administration (FDA) has approved eculizumab (Soliris®), the first product for the treatment of paroxysmal nocturnal haemoglobinuria (PNH), a rare type of blood disorder that can lead to disability and premature death.

PNH, which usually develops in adults, is a disease characterized by red blood cells that develop abnormally. Once the abnormal cells are present in the bloodstream, naturally occurring proteins designed to destroy bacteria and other infection-causing organisms break these cells down. This leads to abnormally darkened urine and, more importantly, causes anaemia. Depending upon the severity of the disorder, patients with PNH may have pain, fatigue and debilitating weakness, the need for frequent blood transfusions, blood clots, and life-threatening or fatal strokes, heart attacks and intestinal disease.

Eculizumab does not cure PNH, but treats the breakdown of red blood cells, the most common characteristic of PNH. Eculizumab blockade of the body's natural immune system increases the patient's susceptibility to certain serious infections, particularly meningococcal infections. Serious meningococcal infection was the most important adverse reaction experienced by patients in clinical studies. Because of the high risk for serious meningococcal infections, all 196 PNH patients in the clinical studies were vaccinated with a meningococcal vaccine; two of them developed meningococcal sepsis.

Reference: *FDA News*, P07-47, 16 March 2007 at http://www.fda.gov

Access to Medicines

Neglected tropical diseases

One sixth of the world's population suffer from one or more neglected tropical diseases such as Buruli ulcer, cholera, cysticercosis, dracunculiasis (guinea-worm disease), foodborne trematode infections, such as fascioliasis, hydatidosis, leishmaniasis, lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis, trachoma and trypanosomiasis, although there are other estimates that suggest the number could be much higher.

Several of these diseases are vector-borne. Populations most affected are often the poorest and most vulnerable and are in tropical and subtropical areas of the world. Some diseases affect individuals throughout their lives, causing a high degree of morbidity and physical disability and, in certain cases, gross disfigurement. Others are acute infections, with transient, severe and sometimes fatal outcomes.

For a large group of these diseases – mainly helminthic infections – effective, inexpensive or donated drugs are available for their prevention and control. However, there is second group which requires systematic case-finding and management at an early stage. Simple diagnostic tools and safe and effective treatment regimens still need to be developed for some of these diseases. For others, vector control is available, as in the case of Chagas disease.

Increased awareness and advocacy are needed to draw attention to the realistic prospect of reducing the negative impact of neglected tropical diseases on the health and social and economic well-being of affected communities.

Reference: WHO Department of Control of Neglected Tropical Diseases at http://www.who.int/neglected_diseases/en/index.html

Open access database for neglected medicines development

An international network of researchers has announced the release of a new web-based resource designed to facilitate the development of medicines to fight infectious diseases afflicting the developing world. The Drug Target Prioritization Database is available at http://TDRtargets.org.

The database is described as a comprehensive set of information pertinent to drug target discovery, for a diverse array of parasitic and bacterial diseases. The Drug Target Prioritization Network was established in 2005 by the Special Programme for Research and Training in Tropical diseases (TDR) of WHO and includes a global team of academic laboratories, research centres and industry scientists, focusing on the pathogens responsible for malaria, tuberculosis, African sleeping sickness, leishmaniasis, Chagas disease and worm infections such as schistosomiasis and filariasis — all of which are in desperate need of new treatments.

Together, these diseases are responsible for billions of infections in the developing world and more than six million deaths per year.

New avenues for drug discovery
The database is unique in that it allows any researcher — in both developed and developing countries — to have access to information on the complete genome sequences for organisms responsible for five tropical diseases, with more anticipated for the parasitic worms known as helminths. Pharmaceutical firms have extensive libraries of chemicals that might act against the disease pathogens. The missing step, which this initiative takes, is to make available a list of proposed and validated drug targets, in addition to allowing users to define their own search criteria. This resource should expedite the time-consuming and high-risk early stages of drug development.

The TDRtargets.org web site combines available genomic and bioinformatic data for each priority organism with automatically extracted and manually curated information from the research literature and other databases relevant to each putative drug target. The network has invested substantial effort in annotation to assist scientists in the identification of high-value drug targets. The database also permits comments from experts in the field.

User-defined weightings permit potential drug targets to be ranked according to their desirability, providing prioritized, customized lists. While this network was developed to facilitate drug target identification, it is also useful for the identification of vaccine and diagnostic targets as well, and could spur fundamental research into areas such as target validation, assay development, biomarkers and drug resistance.

Reference: Special Programme for Research and Training in Tropical diseases (TDR) at http://TDRtargets.org

Consultation Document

International Pharmacopoeia

Artemether and lumefantrine capsules

Draft proposal for the International Pharmacopoeia (March 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax: ++41 22 791 4730 or e-mail to rabhouansm@who.int

Category. Antimalarial.

Storage. Artemether and Lumefantrine capsules should be kept in a well-closed container, protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines: 20 mg Artemether and 120 mg Lumefantrine.

[Note from the Secretariat: Artemether and Lumefantrine capsules are not included in the current WHO Model list of essential medicines, only tablets of above strength.]

Requirements

Complies with the monograph for "Capsules".

Artemether and Lumefantrine capsules contain Artemether and Lumefantrine. They contain not less than 90.0% and not more than 110.0% of the amounts of artemether ($C_{16}H_{26}O_5$) and lumefantrine ($C_{30}H_{32}Cl_3NO$) stated on the label.

Identity tests

A Carry out test A.1 or, where UV detection is not available, test A.2.

A.1. 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 40 volumes of light petroleum R1, 10 volumes of ethyl acetate R and 5 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 μl of each of the following 2 solutions in acetone R. For solution (A) shake a quantity of the contents of the capsules equivalent to about 10 mg Artemether (about 60 mg Lumefantrine) for 5 minutes with 10 ml, filter, and use the clear filtrate. For solution (B) use 1 mg artemether RS and 6 mg lumefantrine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air.

(i) Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity to that obtained with solution B (identifying Lumefantrine).

(ii) Spray the plate with sulfuric acid/methanol TS. Heat the plate for 10 minutes at 140 °C. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity to that obtained with solution B (identifying Artemether).

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 40 volumes of light petroleum R1, 10 volumes of ethyl acetate R and 5 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions in acetone R. For solution (A) shake a quantity of the contents of the capsules equivalent to about 10 mg Artemether (about 60 mg Lumefantrine) for 5 minutes with 10 ml, filter, and use the clear filtrate. For solution (B) use 1 mg artemether RS and 6 mg lumefantrine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Spray with sulfuric acid/methanol TS. Heat the plate for 10 minutes at 140°C, allow it to cool and expose to iodine vapours for 20 minutes. Examine the chromatogram immediately in daylight.

The principal spots obtained with solution A corresponds in position, appearance, and intensity to those obtained with solution B.

B. See the test described below under Assay. The retention times of the two principal peaks in the chromatogram obtained with solution (1) are similar to those in the chromatogram obtained with solution (2).

Artemether-related substances. Protect samples from light, also during chromatography.

Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 40 volumes of light petroleum R1, 10 volumes of ethyl acetate R and 5 volumes of glacial acetic acid R as the mobile phase.

Prepare the following solutions in the solvent consisting of 1 volume of purified water and 1 volume of acetonitrile R. For solution (1), weigh and mix the contents of 20 capsules. To a quantity of the powder containing 100 mg of artemether add 20 ml of the solvent, sonicate for 15 minutes and centrifuge. Filter a portion of the supernatant through a 0.45 µm filter, discarding the first few ml of the filtered solution. For solution (2) dissolve 2 mg of each of artemether RS, dihydroartemisinin (artenimol RS) and á-artemether RS in 20 ml of the solvent. For solution (3) dilute 2.0 ml of solution (2) to 20 ml with the solvent. For solution (4) dilute 3.0 ml of solution (2) to 20 ml with the solvent. For solution (5) dilute 5.0 ml of solution (2) to 20 ml with the solvent. For solution (6) dilute 1.0 ml of solution (2) to 2 ml with the solvent. For solution (7) dilute 3.0 ml of solution (2) to 4 ml with the solvent.

Apply separately to the plate 20 µl of each of the solution (1), (3), (4), (5), (6) and (7). After application allow the spots to dry for 15 minutes in a current of cool air. Develop over a path of 12 cm. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Dip the plate in sulfuric acid/methanol TS. Heat the plate for 10 minutes at 140 °C. Examine the chromatogram in daylight.

Artemether and related substances have the following R_f values: impurity A about 0.25; dihydroartemisinin about 0.3; impurity B about 0.35; α-artemether about 0.4; artemether about 0.55.

In the chromatogram obtained with solution (1):

–any spot corresponding in R_f value to impurity A is not more intense than the spot corresponding to artemether obtained with solution (7) (1.5%);

–any spot corresponding in R_f value to dihydroartemisinin is not more intense than the spot corresponding to dihydroartemisinin obtained with solution (6) (1.0%);

–any spot corresponding in R_f value to impurity B is not more intense than the spot corresponding to artemether obtained with solution (5) (0.5%);

–any spot corresponding in R_f value to á-artemether is not more intense than the spot corresponding to á-artemether obtained with solution (4) (0.3%);

–the spot of any other impurity is not more intense than the spot corresponding to artemether obtained with solution (3) (0.2%). Disregard any spot remaining at the point of application.

Assay. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 3.9 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 ìm) ([1] Symmetry is suitable.)

Use the following conditions for gradient elution:

Mobile phase A: 700 volumes of ion pair reagent and 300 volumes of acetonitrile R.

Mobile phase B: 300 volumes of ion pair reagent and 700 volumes of acetonitrile R.

Prepare the ion pair reagent by dissolving 5.65 g of sodium hexanesulfonate R and 2.75 g of sodium dihydrogen phosphate R in about 900 ml of purified water. Adjust the pH to 2.3 using phosphoric acid (~105 g/l) TS, dilute to 1000 ml and filter through a 0.45 µm filter.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–28	60	40	Isocratic
28–29	60 to 0	40 to 100	Linear gradient
29–45	0	100	Isocratic
45–46	0 to 60	100 to 40	Linear gradient
46–55	60	40	Isocratic re-equilibration

Prepare the following solutions in the solvent which is obtained by mixing 200 ml of ion pair reagent, 60 ml of purified water and 200 ml of 1-propanol R and diluting to 1000 ml with acetonitrile R. For solution (1), weigh and mix the contents of 20 capsules. Transfer a quantity of the powder containing about 20 mg of artemether (about 120 mg of lumefantrine), accurately weighed, to a 100 ml volumetric flask. Add approximately 85 ml of the solvent, sonicate for 20 minutes, allow to cool to room temperature and dilute to volume with the solvent. Filter through a 0.45 μm filter, discarding the first few ml of the filtered solution. For solution (2), accurately weigh 20 mg artemether RS and 120 mg lumefantrine RS in a 100 ml volumetric flask. Add approximately 85 ml of solvent, sonicate until dissolved, allow to cool to room temperature and dilute to volume.

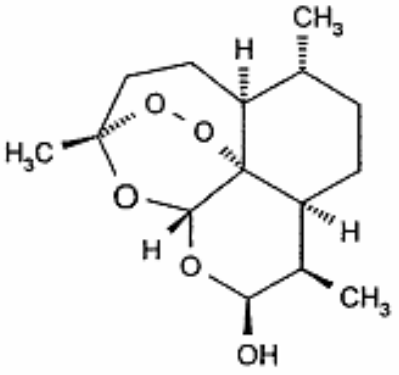
Operate with a flow rate of 1.3 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 210 nm for the first 28 minutes and then switch to about 380 nm.

Inject alternately 20 μl each of solutions (1) and (2). (The peak for artemether is eluted at a retention time of approximately 19 minutes, and that for lumefantrine at a retention time of approximately 34 minutes.)

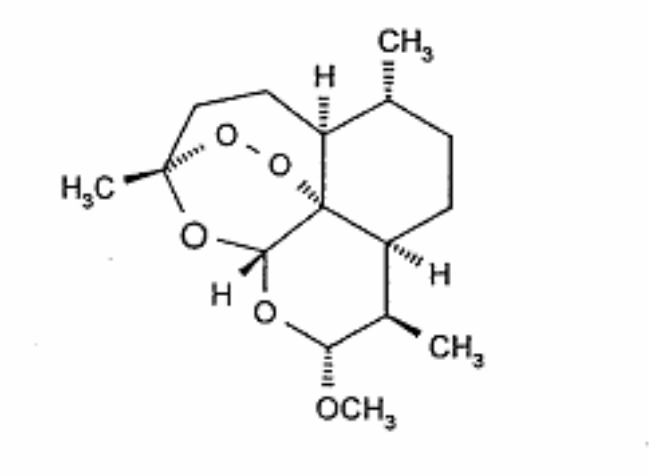
Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of artemether ($C_{16}H_{26}O_5$) and lumefantrine ($C_{30}H_{32}Cl_3NO$).

Impurities (artemether-related)

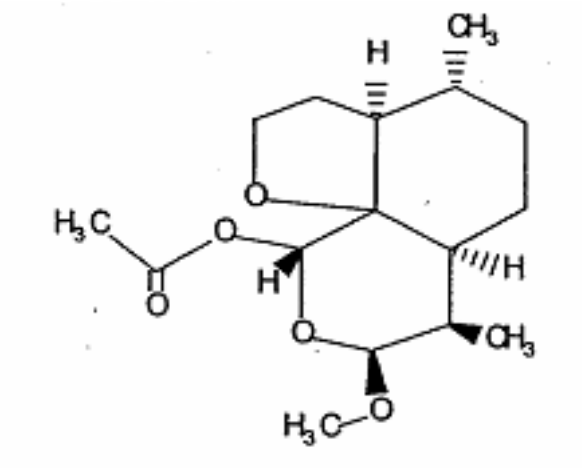
Dihydroartemisinin 284.4 $C_{15}H_{24}O_5$



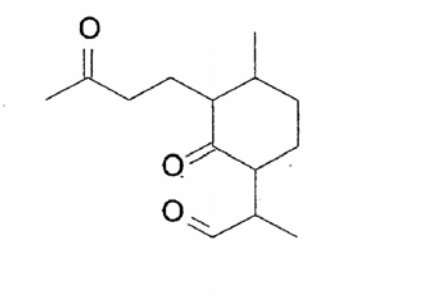
α-artemether 298.4 $C_{16}H_{26}O_5$



B. 298.4 C_{1}



A. 238.3 $C_{14}H_{22}O_3$



[Names to be provided for A and B]

Magnesi sulfatis injectio
Magnesium sulfate Injection

Draft proposal for the International Pharmacopoeia (March 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax: ++41 22 791 4730 or e-mail to rabhouansm@who.int

Note from the Secretariat: Inclusion of a monograph for magnesium sulfate injection is considered advisable in view of the potential for errors in dosage due to confusion concerning the strength of this injection since "Magnesium sulfate" is the heptahydrate (mol wt 246.5 compared with 120 for anhydrous substance). This injection is included in the WHO Model List of Essential Medicines and within the "Making Pregnancy Safer" programme of the Family and Community Health cluster of WHO.

Description. A clear, colourless solution.

Category. Used in the prevention of seizures in eclampsia and pre-eclampsia.

Labelling. The designation of the container of Magnesium sulfate injection should indicate the quantity in terms of the amount of magnesium sulfate heptahydrate and as the approximate concentration of magnesium ions (Mg^{2+}) in millimoles per ml.

Additional information. Strength in the current WHO Model list of essential medicines: 500 mg of magnesium heptahydrate /ml; the concentration of magnesium ions (Mg^{2+}) is approximately
2 millimoles per ml (2 mmolMg^{2+}/ml).

Requirements

Complies with the monograph for "Parenteral Preparations".

Definition. Magnesium sulfate injection is a sterile solution of Magnesium Sulfate Heptahydrate in water for injections. The solution is sterilized by "Heating in an Autoclave" or by another suitable method (see 5.8 Methods of Sterilization).

Magnesium sulfate injection contains not less than 90.0% and not more than 110.0% of the amount of $MgSO_4,7H_2O$ stated on the label.

Identity tests

A. Dilute the injection to give a solution containing 5 mg of magnesium sulfate heptahydrate per ml. To 2 ml of this solution, add 1 ml of ammonia (100g/l) TS; a white precipitate is produced which redissolves after adding 1 ml of ammonium chloride (100g/l) TS. Add 1 ml of disodium hydrogen phosphate (40g/l) TS; a white, fine crystalline precipitate is formed.

B. Dilute the injection to give a solution containing 20 mg of magnesium sulfate heptahydrate per ml; yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

pH value. (1.13) pH of the injection, diluted if necessary to contain 500 mg of magnesium sulfate heptahydrate /ml: 5.5 - 7.0.

Assay. Dilute an accurately measured volume of the injection containing about 0.50 g of magnesium sulfate heptahydrate to 100 ml with water R and proceed with the titration as described under 2.5 Complexometric titrations for magnesium. Each ml of disodium edetate (0.05 mol/l) VS is equivalent to 12.32 mg of $MGSO_4$, $7H_2O$

Zinci sulfas
Zinc sulfate

Zinc sulfate monohydrate
Zinc sulfate heptahydrate

Draft proposal for the International Pharmacopoeia (March 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax: ++41 22 791 4730 or e-mail to rabhouansm@who.int

Note from the Secretariat: Preparation of the zinc monographs was initiated because zinc supplementation is included in the revised the WHO/UNICEF recommendations for the management of diarrhoea as an adjunct to oral rehydration therapy.]

$ZnSO_4,H_2O$ (monohydrate); $ZnSO_4,7H_2O$ (heptahydrate)

Relative molecular mass. 179.5 (monohydrate); 287.5 (heptahydrate).

Chemical name. Zinc sulfate monohydrate; CAS Reg. No. *7446-19-7 (monohydrate).* Zinc sulfate heptahydrate; CAS Reg. No. *7446-20-0 (heptahydrate).*

Description. A white or almost white, crystalline powder, or colourless, transparent crystals.

Solubility. Very soluble in water, practically insoluble in ethanol (~750 g/l) TS.

Category. Adjunct to oral rehydration salts in(prevention and) treatment of dehydration due to diarrhoea; astringent.

Storage. Zinc sulfate should be kept in a well-closed non-metallic container.

Requirements

Definition. Zinc sulfate monohydrate contains not less than 99.0% and not more than 101.0% of $ZnSO_4,H_2O$. Zinc sulfate heptahydrate contains not less than 99.0% and not more than 104.0% of $ZnSO_4,7H_2O$.

Identity tests

A. Dissolve 0.25 g in 5 ml of water R and add 0.2 ml of sodium hydroxide (400 g/l) TS. A white precipitate is formed. Add a further 2 ml of sodium hydroxide (400 g/l) TS. The precipitate dissolves. Add 10 ml of ammonium chloride (100 g/l) TS. The solution remains clear. Add 0.1 ml of sodium sulfite TS. A flocculent white precipitate is formed.

B. A 50 mg/ml solution yields the reactions described under 2.1 General identification tests as characteristic of sulfates.

C. The test substance complies with the limits of the assay.

pH value. (1.13) pH of a 50 mg/ml solution in carbon-dioxide-free water R, 4.4-5.6.

Chlorides. Use 0.83 g in 20 ml for the preparation of the test solution as described under 2.2.1 Limit test for chlorides; not more than 300 ìg/g.

Iron. Use 0.40 g for the preparation of the test solution as described under 2.2.4 Limit test for iron; not more than 100 ìg/g.

Assay

For the monohydrate Dissolve about 80 mg, accurately weighed, in 5 ml of acetic acid (~120 g/l) TS and proceed with the titration as described under 2.5 Complexometric titrations for zinc. Each ml of disodium edetate (0.05 mol/l) VS is equivalent to 8.975 mg of $ZnSO_4,H_2O$.

For the heptahydrate Dissolve about 0.13 g, accurately weighed, in 5 ml of acetic acid (~120 g/l) TS and proceed with the titration as described under 2.5 Complexometric titrations for zinc. Each ml of disodium edetate (0.05 mol/l) VS is equivalent to 1.438 g of $ZnSO_4,7H_2O$.

Paediatric zinc sulfate tablets

Draft proposal for the International Pharmacopoeia (March 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax: ++41 22 791 4730 or e-mail to rabhouansm@who.int

Note from the Secretariat: The term “paediatric” has been used in the title of this monograph since these tablets are included in the WHO Model List of Essential Medicines (revised March 2005) under “medicines for diarrhoea in children” (section17.5.2).

Preparation of the zinc monographs was initiated because zinc supplementation is included in the revised the WHO/UNICEF recommendations for the management of diarrhoea as an adjunct to oral rehydration therapy.

Category. Adjunct to oral rehydration salts in (prevention and) treatment of dehydration due to diarrhoea.

Storage. Paediatric zinc sulfate tablets should be kept in a well-closed container.

Labelling. The designation of the container of Paediatric zinc sulfate tablets should state that the active ingredient is in the monohydrate form and indicate the quantity in terms of the equivalent amount of elemental zinc.

Additional information. Strength in the current WHO Model list of essential medicines: 10 mg of elemental zinc (as zinc sulfate monohydrate).

Requirements

Comply with the monograph for "Tablets".

Definition. Paediatric zinc sulfate tablets contain Zinc Sulfate as the monohydrate in a suitable dispersible basis that may contain suitable flavouring agents. They contain not less than 90.0% and not more than 110.0% of the amount of zinc stated on the label.

Manufacture. The formulation of the tablets and the manufacturing process are designed and controlled so as to ensure that the metallic taste of the zinc salt is adequately masked.

Identity tests. For solution (A) shake a quantity of the powdered tablets containing the equivalent of 100 mg of zinc with 20 ml, filter, and use the clear filtrate.

A. To 5 ml of solution (A) add 0.2 ml of sodium hydroxide (400 g/l) TS. A white precipitate is formed. Add a further 2 ml of sodium hydroxide (400 g/l) TS. The precipitate dissolves. Add 10 ml of ammonium chloride (100 g/l) TS. The solution remains clear. Add 0.1 ml of sodium sulfite TS. A flocculent white precipitate is formed.

B. Five ml of solution (A) yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

Disintegration. Comply with 5.4 Disintegration test for tablets and capsules, operating the apparatus for 60 seconds.

Assay. Weigh and powder 20 tablets. To a quantity of the powder equivalent to about 29 mg of zinc, accurately weighed, add 5 ml of acetic acid (~120 g/l), sonicate for 15 minutes and add about 50 ml water R. Proceed with the titration as described under 2.5 Complexometric titrations for zinc. Each ml of disodium edetate (0.05 mol/l) VS is equivalent to 3.27 mg of zinc.

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Paediatric zinc sulfate oral solution

Draft proposal for the International Pharmacopoeia (March 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax: ++41 22 791 4730 or e-mail to rabhouansm@who.int

Note from the Secretariat: The term "paediatric" has been used in the title of this monograph since these tablets are included in the WHO Model List of Essential Medicines (revised March 2005) under "medicines for diarrhoea in children" (section17.5.2).

Preparation of the zinc monographs was initiated because zinc supplementation is included in the revised the WHO/UNICEF recommendations for the management of diarrhoea as an adjunct to oral rehydration therapy.

Category. Adjunct to oral rehydration salts in (prevention and) treatment of dehydration due to diarrhoea.

Storage. Paediatric zinc sulfate oral solution should be kept in a well-closed container.

Labelling. The designation of the container of Paediatric zinc sulfate oral solution should indicate the quantity in terms of the equivalent amount of elemental zinc.

Additional information. Strength in the current WHO Model list of essential medicines: 10 mg of zinc (as zinc sulfate) per 5 ml.

Requirements

Complies with the monograph for "Liquids for Oral Use".

Definition. Paediatric zinc sulfate oral solution is a solution of Zinc Sulfate as the monohydrate or heptahydrate in a suitable flavoured vehicle. It contains not less than 90.0% and not more than 110.0% of the amount of zinc stated on the label.

Manufacture. The formulation of the oral solution and the manufacturing process are designed and controlled so as to ensure that the metallic taste of the zinc salt is adequately masked.

Identity tests

A. To 5 ml add 0.2 ml of sodium hydroxide (400 g/l) TS. A white precipitate is formed. Add a further 2 ml of sodium hydroxide (400 g/l) TS. The precipitate dissolves. Add 10 ml of ammonium chloride (100 g/l) TS. The solution remains clear. Add 0.1 ml of sodium sulfite TS. A flocculent white precipitate is formed.

B. Five ml yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

pH value. (1.13) pH of the oral solution: 2.5–4.5.

Relative density

Note from the Secretariat: Comment is invited as to whether inclusion of a requirement for relative density is advisable and, if so, what limits would be considered suitable using method 1.3 of Ph. Int. (20 ˚C).

Assay. To a quantity of the oral solution equivalent to about 10 mg of zinc, accurately measured, add 50 ml of purified water and 5 ml of ammonia buffer TS and titrate with disodium edetate (0.01 mol/l) VS using Mordant Black 11 indicator mixture R as indicator. Each ml of disodium edetate (0.01 mol/l) VS is equivalent to 0.6539 mg of zinc.

Recent Publications, Information and Events

Informed consent for research in resource-poor settings

Ethical challenges in study design and informed consent for health research in resource-poor settings considers ethical challenges to research design and informed consent in biomedical and behavioural studies conducted in resource-poor settings. A review of the literature explores relevant social, cultural, and ethical issues in the conduct of biomedical and social health research in developing countries. Ten case vignettes illustrate ethical challenges that arise in international research with culturally diverse populations.

Professional and public debates concerning the application of guidelines for ethical conduct in studies carried out in developing countries are likely to continue as new information becomes available. Researchers in biomedicine, public health, and the social and behavioural sciences confront the challenging task of adhering to national and international regulations in social and cultural environments in which ethical guidelines may not be easily translated or applied. Increased awareness of ethical concerns associated with study design and informed consent among researchers working in resource-poor settings is needed. But strengthening professional knowledge about international research ethics is not enough. Investigators also require practical advice on the best methods or models for articulating ethical guidelines in the field. Empirical research on a wide range of issues relevant to the application of ethical guidelines is needed, including studies of macro social and economic developments that drive the globalization of the biomedical research enterprise.

Technological and financial resources are also necessary to build capacity for local collaborators and communities to ensure that results of research are integrated into existing health systems. This requires collaborative efforts and engaged commitment on the part of investigators, funding agencies, policy-makers, governmental institutions, and industry.

Reference: Ethical challenges in study design and informed consent for health research in resource-poor settings http:// www.who.int/tdr/publications/publications/seb_topic5.htm

UNDP/WorldBank/WHO-TDR http://www.who.int/tdr/topmenu/news/

Lessons learned in home management of malaria

Implementation research in four African countries

Studies on treatment-seeking behaviour have shown that most malaria episodes are first treated at home using shop-bought drugs. Part of the reason for this is poor access to formal health services. These treatments may be incorrect or suboptimal. Since the majority of children who die from malaria do so within 48 hours of onset of illness, the early use of effective antimalaria medicines close to the home can help to reduce the burden of the disease in sub-Saharan Africa and minimize the life-threatening consequences of treatment delays.

This guide focuses in particular on four countries – Burkina Faso, Ghana, Nigeria and Uganda – where country teams have completed community based studies in home management of malaria.

Reference: World Health Organization. Lessons learned in Home Management of Malaria. Implementation research in four African countries, 2007

Developing drug information centres in India

A unique training workshop was organized in Bangalore in December 2006. Participants from India were provided with an introduction to drug information practice and rational drug use. The course was a part of a programme to expand the influence of the drug information centres and clinical pharmacy training programmes which have developed in the south of India over the last ten years.

The current programme is being coordinated by the Karnataka State Pharmacy Council (KSPC) and is funded by WHO (India Office). KSPC established a drug information centre in 1997 and also works with hospital-based clinical pharmacy training programs in Bangalore. Other departments of pharmacy practice in south India include drug information training in their clinical programs and offer independent information to clinicians within their institutions.

The centres will provide information to healthcare professionals and the public, and will collect reports of suspected adverse drug reactions. Limited funding will be provided to purchase information resources but long-term support will be required at the state level.

Reference: FIP pharmacy information section newsletter. March 2007 www.fip.org

First–in–man clinical trials for high risk products

European Union — The Committee for Medicinal Products for Human Use (CHMP) has adapted a draft guideline for first-in-man clinical trials for potential high-risk medicinal products. This guideline has been prepared as one of the measures for minimizing the risk of serious adverse reactions of the nature that occurred during the first-in-man clinical trials of TGN1412 (gene therapy). It gives guidance on managing the transition from non-clinical studies to first tests in humans for high-risk medicinal products. The draft guideline has been released for a two-month public consultation.

Reference: Press Release. EMEA, 26 March 2007. http://www.emea.europa.eu

Pakistan Pharmacists Society discussion forum

The Pakistan Pharmacists Society promotes and expands the profession of pharmacy and the role of pharmacists. In order to improve drug use and pharmacy practice in the country, the Society has launched a website to serve as an online source of news, pharmacy jobs, and to provde an opportunity for pharmacists to link up, share ideas and develop activities of interest.

Reference: Pakistan Pharmacists Society (PPS) http:// www.pharmacist.pk and http:// www. pharmacy.org.pk

New quality assurance compendium

Over the years, WHO's Expert Committee on Specifications for Pharmaceutical Preparations has made numerous recommendations to establish standards

and guidelines and to promote the effective functioning of national regulatory and control systems and implementation of internationally agreed standards.

Many of the relevant documents endorsed by the Expert Committee are reproduced in a recently published compendium of guidelines and related materials *Quality Assurance of Pharmaceuticals. Second Edition* aiming to provide information covering all aspects of WHO good manufacturing practices and inspection. The compendium includes.

1. WHO good manufacturing practices: main principles for pharmaceutical products

- Quality management in the drug industry: philosophy and essential elements
- Heating Ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms
- Validation
- Water for pharmaceutical use

2. WHO good manufacturing practices: starting materials

- Active pharmaceutical ingredients (bulk drug substances)
- Pharmaceutical excipients

3. WHO good manufacturing practices: specific pharmaceutical products

- Sterile pharmaceutical products
- Biological products
- Investigational pharmaceutical products for clinical trials in humans
- The manufacture of herbal medicines
- Radiopharmaceutical products

4. Inspection

- Pre-approval inspections
- Inspection of pharmaceutical manufacturers
- Inspection of drug distribution channels
- Quality systems requirements for national good manufacturingbpractice inspectorates
- Guidance on good manufacturing practices: inspection report
- Model certificate of good manufacturing practices

5. Hazard and risk analysis in pharmaceutical products

- Application of hazard analysis and critical control point (HACCP) methodology to pharmaceuticals

6. Sampling operations

- Sampling of pharmaceutical products and related materials

Reference: Quality Assurance of Pharmaceuticals. Second Edition. http://www.who.int/bookorders

Pharmacological management of human H5N1 infection

The recent geographical spread of highly pathogenic avian influenza A virus in poultry and wild waterfowl has increased opportunities for transmission of the H5N1 virus to humans. Outbreaks in poultry have now been accompanied by human cases in nine countries. To date, human cases have remained rare and sporadic, but the disease is very severe and the case fatality is high. With the H5N1 virus now confirmed in birds in more than 50 countries, additional sporadic human cases should be anticipated.

Although international experts agree that antiviral drugs should be considered for treatment of H5N1 patients and also for chemoprophylaxis, the efficacy and effectiveness of these management options have not been systematically assessed. Guidance on their use is needed worldwide.

In March 2006, the World Health Organization (WHO) convened an international panel of clinicians experienced in the treatment of H5N1 patients, infectious disease experts, public health officers and methodologists to develop rapid advice for the pharmacological management of patients with H5N1 infection. To develop evidence-based guidelines, the panel used a transparent methodological guideline process, based on the GRADE approach, that included evaluation of existing systematic reviews, literature searches and expert consultation. The resulting guidelines separate strong from weak recommendations for or against a specific action and assign four categories of quality of evidence (high, moderate, low and very low).

The panel considered several different specific patient and exposure groups and made a number of strong recommendations for or against specific actions regarding the treatment and chemoprophylaxis of H5N1 virus infection. All recommendations are specific to the current pre-pandemic situation. Recommendations were based on careful consideration of the benefits, harms, burdens and cost of interventions. Risk categorizations for exposure were developed to assist countries in prioritizing the use of antiviral drugs where their availability is limited.

Overall, the quality of the underlying evidence for all recommendations was very low. No data from controlled clinical trials of H5N1 infection are available. The existing evidence is based on small observational case series of H5N1 patients, results from in vitro and animal model studies of H5N1, or the extrapolation of data from high quality studies conducted to evaluate the treatment and chemoprophylaxis of normal, or "seasonal", influenza. These shortcomings highlight the need for further research. While the quality of the evidence for some of the critical outcomes was moderate or low, the overall quality of evidence on which to base a summary assessment was very low for all antiviral drugs. Differences exist in the quality of evidence for individual critical outcomes among the various antiviral drugs (annex 3 sets out the gradings and ratings).

Reference: World Health Organization. *WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus*. WHO/PSM/PAR/2006 at http://www.who.int/medicines