

# WHO Drug Information

## Contents

### Cooperation

- 435** CIOMS - A nongovernmental organization in official relations with WHO

### Pharmacopoeial standards

- 440** Ensuring the efficacy of a deworming medicine: albendazole chewable tablets

### Quality of medicines

- 446** The WHO CPP Scheme in today's regulatory environment – is it time for change?

### Safety news

#### 451 Restrictions

Mirabegron

#### 451 Safety warnings

Proton pump inhibitors • Antiviral combinations for hepatitis C • Daclatasvir hydrochloride and asunaprevir • Vemurafenib • Crizotinib • Fingolimod • Aripiprazole • Sodium polystyrene sulfonate • Iodine-containing contrast agents

#### 454 Known risks

Magnesium oxide • Canagliflozin • Mycophenolate • Ceftriaxone • Roxithromycin • Strontium • Clozapine • Dimethyl fumarate and other fumarate-containing medicines

#### 456 Unchanged recommendations

Clopidogrel • Human papillomavirus vaccines • Entacapone

#### 457 Removal of class warnings

HIV medicines class warnings about lipodystrophy and lactic acidosis removed

#### 457 Safety reviews started

#### 458 Packaging

Improved packaging for dementia treatments

#### 458 Medicines quality

Apotex • Dibotermim alfa-containing implant kit

#### 459 Falsified product alert

Falsified emergency contraceptive circulating in East Africa

### Regulatory news

#### 460 Pre-market assessment

Accelerated access pathways in Europe

#### 460 Regulatory systems

New Zealand working on new regulatory regime

#### 460 Post-marketing control

EMA initiative to improve patient registries

#### 461 Collaboration and harmonization

ICH announces organizational changes • China and WHO collaborate on medicines quality • Meeting of World Pharmacopoeias held in China • Regulators of United Kingdom and India sign agreement • EMA and WHO share non-public information

#### 463 Approved

Insulin degludec & insulin aspart • Efmoroctocog alfa • Modified antihaemophilic factor (recombinant) • Coagulation Factor X (human) • Patiromer • Elvitegravir & cobicistat & emtricitabine & tenofovir alafenamide • Uridine triacetate • Trifluridine & tipiracil • Blinatumomab • Necitumumab • Cobimetinib • Irinotecan liposome injection • Carfilzomib • Ixazomib • Talimogene laherparepvec • Mepolizumab • Osimertinib • Daratumumab • Cariprazine • Pitolisant • Naloxone nasal spray • Idarucizumab • Patiromer

#### 468 EMA Article 58 positive opinion

Pyronaridine-artesunate – paediatric antimalarial formulation

#### 469 Extensions of indications

Anthrax vaccine adsorbed • Ipilimumab • Nivolumab • Pembrolizumab

#### 469 WHO endorsements

Global Ebola virus and antibody reference standards • Malaria vaccine to be delivered in pilot projects

### Publications and events

#### 471 Development

Sustainable development goals aim at health for all

#### 471 Access to medicines

WHO publishes updated essential medicines lists • Medicines Patent Pool expands mandate to hepatitis C and tuberculosis • First patent pool licence for a hepatitis C medicine • Controlled substances not accessible to all in need • Inefficiencies in the global insulin market

*Continued*

*Continued***474 Health and trade**

European Council resolution defends public health interests • HAI/MSF report on EU trade policies and public health • WTO extends drug patent exemption for least-developed countries • New WHO publication about trade and health

**475 Diseases**

Hepatitis world summit adopts Declaration • Malaria death rates plunge but risk remains • Tuberculosis remains a public health challenge • Ebola still a public health emergency • Measles immunization gap persists

**477 Antiretroviral treatment**

WHO recommends treatment for all people living with HIV • Updated optimal list of ARVs for children

**478 Antibiotics**

International summit on antibiotic resistance • Use of veterinary antibiotics in Europe • Multi-country survey reveals misconceptions on antibiotic resistance

**479 Lists and manuals**

Indicators to assess pharmacovigilance systems • Specifications for selected HIV diagnostics

**480 WHO matters**

WHO launches independent assessment of snake antivenoms • WHO Expert Committees on medicines meet in Geneva • New web site on substandard and falsified medicines

**Consultation documents****482 *The International Pharmacopoeia***

**482** Cycloserine

**486** Cycloserine capsules

**490** Ceftriaxone sodium

**493** Ceftriaxone for injection

**ATC/DDD classification**

**496** ATC/DDD classification (temporary)

**501** ATC/DDD classification (final)

**International Nonproprietary Names (INN)**

**503** Proposed INN: List 114

**Abbreviations and web sites**

CHMP	Committee for Medicinal Products for Human Use (EMA)
EMA	European Medicines Agency ( <a href="http://www.ema.europa.eu">www.ema.europa.eu</a> )
EU	European Union
FDA	U.S. Food and Drug Administration ( <a href="http://www.fda.gov">www.fda.gov</a> )
Health Canada	Federal department responsible for health product regulation in Canada ( <a href="http://www.hc-sc.gc.ca">www.hc-sc.gc.ca</a> )
MHLW	Ministry of Health, Labour and Welfare, Japan
MHRA	Medicines and Healthcare Products Regulatory Agency, United Kingdom ( <a href="http://www.mhra.gov.uk">www.mhra.gov.uk</a> )
Medsafe	New Zealand Medicines and Medical Devices Safety Authority ( <a href="http://www.medsafe.govt.nz">www.medsafe.govt.nz</a> )
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
PMDA	Pharmaceuticals and Medical Devices Agency, Japan ( <a href="http://www.pmda.go.jp/english/index.htm">www.pmda.go.jp/english/index.htm</a> )
Swissmedic	Swiss Agency for Therapeutic Products ( <a href="http://www.swissmedic.ch">www.swissmedic.ch</a> )
TGA	Therapeutic Goods Administration, Australia ( <a href="http://www.tga.gov.au">www.tga.gov.au</a> )
U.S.	United States of America

**Note:**

The online version of this issue (available at [www.who.int/medicines/publications/druginformation](http://www.who.int/medicines/publications/druginformation)) has direct clickable hyperlinks to the documents and web pages referenced.

# Cooperation

## CIOMS - A nongovernmental organization in official relations with WHO

**The Council for International Organizations of Medical Sciences (CIOMS) aims to facilitate and promote international activities in the field of biomedical sciences, in collaboration with the United Nations (UN) and WHO. CIOMS has initiated and coordinated major long-term programmes around the topics of *Health Policy, Ethics and Human Values - An International Dialogue* and *International Nomenclature of Diseases*. Currently the main activities are within the areas of bioethics and drug development and use.**

### Background

The Council for International Organizations of Medical Sciences (CIOMS)<sup>1</sup> was established by the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949. Its offices are located in Geneva, close to WHO and the UN Palais des Nations. CIOMS has enjoyed excellent relations with both its “parents” since its creation and is in official relations with WHO and an associate partner of UNESCO.

Through its membership, CIOMS is representative of the biomedical scientific community. The members of CIOMS include international and national professional associations, representing many of the biomedical disciplines, national academies of sciences and medical research councils (*Annex 1*). WHO is represented by at least one senior staff member in all CIOMS working groups. CIOMS also cooperates with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

(ICH) and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA).

### Activities

In its more than six decades of existence, CIOMS has fostered a unique cooperation between specialized international medical associations and societies and other relevant stakeholders, and has promoted global activities in certain areas of the medical sciences whenever international cooperation is called for. CIOMS seeks to take into account the priorities, needs and resources of both industrialized and low-and-middle income countries (LMICs). As a nongovernmental organization, it is also able to draw on the considerable expertise existing in the research-based pharmaceutical industry where appropriate.

### Bioethics

In the field of biomedical research involving human subjects, the World Medical Association (WMA) and CIOMS have been among the key international actors. In addition, the WHO input to

---

<sup>1</sup> [www.cioms.ch](http://www.cioms.ch)

CIOMS activities in the field of research ethics is significant. A major output of this work have been the successive versions of the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (1). First issued in 1982 and revised in 1993 and 2002, these guidelines have been conceived to facilitate the practical implementation of the WMA's Declaration of Helsinki (2) in WHO Member States, including low and middle income countries.

A public consultation is ongoing for an update of these guidelines in line with recent developments, including the revision of the Declaration of Helsinki in 2013. The proposed revised text integrates the previous guidelines for biomedical research and those for epidemiological research (3) in one document. The draft text covers 25 distinct areas (Box 1), and is available for comments until 1<sup>st</sup> March 2016. This is a valuable opportunity for non-commercial research groups to provide their input.

**Box 1. Proposed updated CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects**

► Available for public comment until 1<sup>st</sup> March 2016\*

- Guideline 1 Social value
- Guideline 2 Research conducted in low-resource settings
- Guideline 3 Equitable distribution of benefits and burdens in the selection of groups of participants in research
- Guideline 4 Potential benefits and risks of research
- Guideline 5 Choice of control in clinical trials
- Guideline 6 Caring for participants' health needs
- Guideline 7 Community engagement
- Guideline 8 Collaborative partnership and capacity building for research and review
- Guideline 9 Individual informed consent
- Guideline 10 Modifications and waivers of informed consent
- Guideline 11 Use of stored biological materials and related data
- Guideline 12 Use of health-related data in research
- Guideline 13 Reimbursement and compensation for research participants
- Guideline 14 Treatment and compensation for research-related harms
- Guideline 15 Research involving vulnerable persons
- Guideline 16 Research involving individuals who are not capable of giving informed consent
- Guideline 17 Research involving children and adolescents
- Guideline 18 Women as research participants
- Guideline 19 Pregnant women and lactating women as research participants
- Guideline 20 Research in disaster situations
- Guideline 21 Implementation research
- Guideline 22 Use of online information
- Guideline 23 Research ethics committees and review
- Guideline 24 Public accountability
- Guideline 25 Conflicts of interest

\* <http://www.cioms.ch/index.php/guidelines-test>

**Box 2. Drug development and use: examples of CIOMS documents\***

- Management of drug safety data in the pre-and post-approval phases (4, 5)
- Adverse drug reaction terminology and reporting (6)
- International reporting of adverse drug reactions ([CIOMS I reporting form](#)\*\*)
- Pharmacogenetics (7)
- Clinical pharmacology (8)
- Pharmacovigilance in resource-limited countries (9)
- Vaccine pharmacovigilance (10)
- Practical aspects of signal detection in pharmacovigilance (11)
- Practical approaches to risk minimization for medicinal products (12)

\* The CIOMS publications are available through the web sites of CIOMS and WHO (see footnotes on the next page)

\*\* [www.cioms.ch/index.php/cioms-form-i](http://www.cioms.ch/index.php/cioms-form-i)

**Drug development and use**

CIOMS contributes significantly to the field of drug development and use. Its programme on drug development includes a series of working groups and other projects, which have addressed some fundamental topics and a wide range of issues centered around harmonizing the views of international systems and terminologies used for the safety surveillance of medicinal products and vaccines between stakeholders (**Box 2**). Some of the documents emanating from this work have served as a basis for ICH development and have led to the adoption of regulatory documents in WHO Member States.

Given the aim of harmonization, it has been crucial to collaborate with all stakeholders. The independent status of CIOMS has permitted it to coordinate the contributions and expertise of senior scientists from research-based biopharmaceutical companies, national drug regulatory authorities, academia, and representative bodies of medical specialties to this harmonizing and strengthening of drug-safety surveillance measures. Scientists are invited to

contribute based on their recognized specific expertise and, if required, in consultation with their background institution. Members and consulted experts and their affiliations are listed in the publications.

**CIOMS publications**

The consensus reports and documents discuss and recommend general principles and do not focus on individual medicinal products. As the CIOMS working groups have no legal jurisdiction or mandate to make binding decisions, reliance is placed on other bodies to incorporate the CIOMS recommendations, guidelines or good practices into a regulatory or legislative framework.

Two publications created by CIOMS working groups are expected to be finalized in 2015: a publication by the CIOMS Working Group X on meta-analysis practices for clinical safety data, and an update of the report on *Development and Rational Use of Standardised MedDRA® Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA* (6). For 2016, a series of publications around vaccine safety and

communication is expected from a CIOMS Working Group on Vaccine Safety which was established in 2013 and is linked to WHO's Global Vaccine Safety Initiative (GVSII).

The findings and recommendations of groups convened under the auspices of CIOMS are widely disseminated. Many are available for ordering in printed form<sup>2</sup>, while others can be consulted online and in several cases downloaded without charge<sup>3</sup>. CIOMS publications can also be purchased directly from the CIOMS Secretariat, from WHO<sup>4</sup>, or from specialized bookshops. It should be emphasized that while the sole official versions of all CIOMS reports and guidelines are in English, several publications have been translated into other languages, generally at no cost to CIOMS.

## References

- 1 International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2002.
- 2 World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053.
- 3 International Ethical Guidelines on Epidemiological Studies. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2009.
- 4 Development Safety Update Report (DSUR) Harmonizing the Format and Content for Periodic Safety Report during Clinical Trials: Report of CIOMS Working Group VII. Geneva: Council for International Organizations of CIOMS, 2006.
- 5 Management of Safety Information from Clinical Trials: Report of CIOMS Working Group VI. Geneva: CIOMS, 2005.
- 6 Development and Rational Use of Standardised MedDRA Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA. Geneva: CIOMS, 2004.
- 7 Pharmacogenetics : Towards improving treatment with medicines (Report of the CIOMS Working Group). Geneva: CIOMS, 2005.
- 8 WHO, IUPHAR, CIOMS. Clinical Pharmacology in Health Care, Teaching and Research. Geneva: CIOMS, 2012.
- 9 Current Challenges in Pharmacovigilance: Pragmatic Approaches. Report of CIOMS Working Group V. Geneva: CIOMS, 2013.
- 10 Definitions and Applications of Terms for Vaccine Pharmacovigilance. Geneva: CIOMS, 2012.
- 11 Practical Aspects of Signal Detection in Pharmacovigilance: Report of CIOMS Working Group VIII. Geneva: CIOMS, 2010.
- 12 Practical approaches to risk minimisation for medicinal products: Report of CIOMS Working Group IX. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2014.

<sup>2</sup> CIOMS Available Publications: <http://www.cioms.ch/index.php/publications/available-publications/540/showCategory>

<sup>3</sup> CIOMS Printable Publications: <http://www.cioms.ch/index.php/publications/printablev3/541/showCategory>

<sup>4</sup> WHO Bookshop. [www.who.int/bookorders](http://www.who.int/bookorders)

**Annex 1: CIOMS membership****International members**

- World Allergy Organization
- International College of Angiology
- International Society of Audiology
- International Union of Basic and Clinical Pharmacology (IUPHAR)
- International Association of Bioethics
- International Society of Internal Medicine
- International Federation of Otorhinolaryngological Societies
- World Association of Societies of Pathology and Laboratory Medicine (WASPaLM)
- International Society for Pharmacoepidemiology (ISPE)
- International Society of Pharmacovigilance (ISOP)
- World Psychiatric Association
- International Rhinologic Society
- Medical Women's International Association
- World Medical Association

**National members**

- Comité des Académies Royales de Médecine, Belgium
- Union of the Scientific Medical Societies of Bulgaria
- Czech Medical Association, Czech Republic
- Association of the Scientific Medical Societies in Germany
- The Israel Academy of Sciences and Humanities, Israel
- Korean Academy of Medical Sciences, Republic of Korea
- Islamic Organization for Medical Sciences (IOMS), Kuwait
- Royal Netherlands Academy of Arts and Sciences, Netherlands
- The Research Council for Norway/  
The National Committee for Medical Research Ethics, Norway

- South African Medical Research Council, South Africa
- Swiss Academy of Medical Sciences, Switzerland

**Associate members**

- Medical Sciences Society (MSS-UQ) of Queensland University, Haiti
- American Society for Bioethics and Humanities
- Consulta di Bioetica
- World Federation of Chiropractic
- International Federation of Clinical Chemistry and Laboratory Medicine
- World Organization of Family Doctors (WONCA)
- Good Clinical Practice - Alliance
- International Council for Laboratory Animal Science (ICLAS)
- International Society of Hepatic Encephalopathies & Nitrogen Metabolism (ISHEN)
- Academy of Medical, Dental and Pharmaceutical Sciences of Japan
- The World Association for Medical Law
- International Union of Microbiological Societies
- Asia Pacific Academy of Ophthalmology
- International Union of Physiological Sciences
- Federation of Polish Medical Organizations Abroad
- Federation of Polish Medical Societies
- International Medical Sciences Academy
- National Fund for Scientific Research (NSFR)
- International Federation of Medical Student Associations

► Source: <http://www.cioms.ch/index.php/2012-06-07-19-16-08/membership> ●



# Pharmacopoeial standards

## Ensuring the efficacy of a deworming medicine: albendazole chewable tablets

Parasitic infections affect more than a billion people worldwide, many of them children. Albendazole chewable tablets are an effective treatment and can be administered by non-medical staff such as parents and teachers. However, chewable tablets are sometimes swallowed whole, either intentionally or unintentionally. *The International Pharmacopoeia* therefore requires that chewable tablets – like conventional tablets – comply with the tests for disintegration and dissolution. The monograph included in *The International Pharmacopoeia* for albendazole chewable tablets was revised recently. It provides publicly available quality standards, including a new test for the dissolution of these widely used tablets.

### Ensuring pharmaceutical quality of essential medicines

Pharmacopoeial standards help ensure the quality and safety of essential medicines by providing analytical methods and appropriate limits for testing and assessing the active pharmaceutical ingredients, excipients and finished products.

*The International Pharmacopoeia*<sup>1</sup> focuses on specifying the quality of essential medicines, i.e. those medicines that satisfy the health care needs of the majority of the population in WHO Member States. It underpins some of WHO's most important activities, including those

carried out by the WHO Prequalification Team: medicines and the Department of Control of Neglected Tropical Diseases, to assess and test the quality of medicines found in:

- the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children;
- invitations to manufacturers to submit an expression of interest for product evaluation to the World Health Organization (WHO) Prequalification Team: medicines; and/or
- other United Nations/WHO documents recommending the use of specific medicines for treating specific diseases and/or for use by treatment programmes.

<sup>1</sup> Publicly available at: <http://apps.who.int/phint/en/p/about/>

*WHO provides The International Pharmacopoeia free of charge for WHO Member States to enable quality control testing of active ingredients and finished pharmaceutical products. An example of how these global specifications provide added value for WHO Member States was published in a previous edition of this journal\*.*

*In 2015, publication of the Fifth Edition of The International Pharmacopoeia (Ph. Int.) and the 50<sup>th</sup> annual meeting of the WHO Expert Committee which is mandated to keep it relevant and updated, represented two major landmarks. The paper presented here describes another example of a monograph, newly included in the Fifth Edition of Ph. Int., that contributes to bringing affordable, safe and efficacious medicines of good quality to everyone, everywhere.*

\* *Global specifications: the example of capreomycin. WHO Drug Information 2014; 28(4):431-3.*



Priority is placed on monograph development for essential medicines that are not included or not sufficiently described in other pharmacopoeias. Many of these medicines are needed urgently, either because current production does not cover global treatment needs or because available products are not quality-assured. Albendazole chewable tablets is one such medicine.

### **Albendazole: a needed treatment**

Albendazole is an effective treatment for a range of parasitic diseases that represent a significant public health burden, as described below.

#### **Lymphatic filariasis**

Lymphatic filariasis, commonly known as elephantiasis, is a neglected tropical disease. It is caused by parasitic infection with nematodes (roundworms) of the family *Filariodidea* that are transmitted by mosquitoes. It is usually acquired in childhood and damages the lymphatic system. The painful and profoundly disfiguring visible manifestations of the disease occur later in life and lead to permanent disability. Patients are not only physically disabled, but suffer mental, social and financial losses contributing to stigma and poverty.

Currently, 1.23 billion people in 58 countries live in areas where lymphatic filariasis is transmitted and are at risk of being infected.

► Lymphatic filariasis can be eliminated by stopping the spread of the infection through use of large-scale chemoprevention, consisting of a single dose of two medicines — albendazole chewable tablets (400 mg) together with ivermectin tablets (150–200 µg/kg) or with diethylcarbamazine tablets (DEC)

(6 mg/kg) — given annually to an entire at-risk population. (1)

#### **Soil-transmitted helminth infections**

Soil-transmitted helminth infections are among the most common infections worldwide. They are transmitted by eggs present in human faeces which in turn contaminate soil especially in areas where sanitation is poor. The main species that infect people are the roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*) and hookworms (*Necator americanus* and *Ancylostoma duodenale*).

More than 1.5 billion people, or 24% of the world's population, are infected with soil-transmitted helminth infections. Over 270 million preschool-age children and over 600 million school-age children live in areas with high transmission rates of these parasites and are in need of treatment and preventive interventions.

► The WHO recommended medicines — albendazole chewable tablets and mebendazole chewable tablets — are effective, inexpensive and easy to administer by non-medical personnel, for example teachers. (2)

### **Chewable tablets: a question of definition**

Pharmacopoeias define chewable tablets differently. The definitions deviate from each other in particular with regard to administration (*must* be chewed or *may* be chewed) and, consequently, not all pharmacopoeias require a disintegration test (Box 1). In *The International Pharmacopoeia*, a disintegration requirement has been included to address concerns about the efficacy of chewable tablets that are swallowed whole, either intentionally or unintentionally.

## The need for dissolution testing

Monographs for solid oral dosage forms in *The International Pharmacopoeia* usually contain a dissolution test and/or a disintegration test. The choice of testing disintegration or dissolution for a given product is based on international standards such as the International

Council for Harmonisation (ICH) guideline on Test Procedures and Acceptance Criteria for New Drug Products (3). This guideline advises that disintegration testing may be sufficient for rapidly dissolving medicines containing active ingredients that are highly soluble in the body. For albendazole chewable tablets,

### Box 1. Definition of chewable tablets and disintegration requirements in different pharmacopoeias

- The **European Pharmacopoeia** (Ph. Eur. 8.7) states in the general monograph on tablets that *“Chewable tablets are intended to be chewed before being swallowed.”* As chewable tablets are not exempted from the test for disintegration of uncoated (or coated) tablets, they are required to comply with the test for disintegration.
- The **British Pharmacopoeia** (2016) includes the general monograph on tablets of the European Pharmacopoeia and would thus require that (uncoated or coated) chewable tablets comply with the test for disintegration. However, the requirement for disintegration usually does not apply either because the individual monographs on chewable tablets explicitly mention this or because a requirement for dissolution eliminates the need for a disintegration test (see also chapter entitled “Tablets” of the British Pharmacopoeia).
- The **United States Pharmacopoeia** (USP 38) states (in the section on tablets that is included in the general chapter on Pharmaceutical Dosage Forms <1151>) that *“tablets [...] that include ‘chewable’ in the title must be chewed or crushed prior to swallowing to ensure reliable release of the drug substance(s) or to facilitate swallowing. If tablets are designed so that they may be chewed (but chewing is not required for drug substance release or ease of swallowing), the title should not include a reference to ‘chewable’.”* Following this definition, chewable tablets are exempted from the disintegration test: *“Chewable tablets are not required to comply with the disintegration test”* (section on chewable tablets in the general chapter: <2> Oral Drug Products – Product Quality Tests).
- The general chapter on tablets in the **Indian Pharmacopoeia** (2014) determines that the disintegration requirement for uncoated and coated tablets does not apply to chewable tablets. In the section on “Tablets for Use in the Mouth” it is stated that *“where applicable the tablets should be chewed before swallowing”*.
- The **Chinese Pharmacopoeia** (2010) specifies that *“chewable tablets are tablets intended to be chewed and then swallowed”* and that *“chewable tablets may not be required to comply with the test for disintegration.”* (Appendix I, General Requirements for Preparations).
- According to **The International Pharmacopoeia** (Fifth Edition), chewable tablets are usually uncoated, and as such they have to disintegrate within 15 minutes (see general monograph on Tablets). This requirement was included to address concerns about the efficacy of chewable tablets that are swallowed whole. This may occur either intentionally or unintentionally. Accordingly, *The International Pharmacopoeia* defines chewable tablets as tablets that *“are intended to be chewed before being swallowed; however, where indicated on the label, they may be swallowed whole instead”*.

however, disintegration testing cannot replace dissolution testing as the solubility of albendazole at 37°C throughout the physiological pH range (pH value 1–7.5) is reported to be low (4, 5).

Compendial dissolution tests provide information about the drug-release characteristics of a particular formulation, or batch of a product, under standardized test conditions. Compliance with a dissolution test provides assurance that most of the active ingredient will dissolve in an aqueous medium within a reasonable amount of time when the preparation is subject to mild agitation. However, compliance with a dissolution test does not in itself guarantee bioavailability. Failure to comply with a dissolution test, on the other hand, may indicate that the bioavailability of the product is too low, since the active substance must be released from the dosage form for any local or systemic pharmacological activity to occur.

Surveys have shown that the dissolution properties of albendazole chewable tablets on the market are poor. In 2011 a survey of medicines for neglected tropical diseases showed that 57% of the products tested failed to comply with dissolution test requirements (6). A more recent study, performed in Ethiopia, produced similar results, with 8 of 19 tested albendazole tablets (42%) failing to comply with the dissolution test (7).

Investigations suggest that albendazole chewable tablets that pass disintegration and *in vitro* dissolution tests have better clinical effects, measured as cure rates and egg reduction rates for *Ascaris lumbricoides*, *Trichuris trichiura* and hook-worm infections, than those that fail these tests (8). Although the clinical implications of failure to comply with dissolution test requirements need to be evaluated in

detail, it is very likely that the efficacy of albendazole tablets is compromised if the ingredients are not released from the tablets. A publicly available test method to verify the dissolution properties of albendazole chewable tablets is therefore urgently needed.

### Setting up the dissolution requirements

Most guidance documents on dissolution testing require that chewable tablets – the whole tablets, not the crushed tablets – are subjected to *in vitro* dissolution testing (9). The FIP/AAPS guidelines (10) state: *“In principle, the test procedure employed for chewable tablets should be the same as that for regular tablets. This concept is based on the possibility that a patient might swallow the dosage form without proper chewing, in which case the drug will still need to be released to ensure the desired pharmacological action.”* However, *“because of the non-disintegrating nature of the dosage form, there may be a necessity to alter test conditions (e.g. increase the agitation rate) and specifications (e.g. increase the test duration).”*

To elaborate a dissolution test for albendazole chewable tablets for inclusion in *The International Pharmacopoeia* samples of albendazole chewable tablets were investigated for their *in vitro* release of the active ingredient. The product chosen for this investigation was the comparator product recommended for bioequivalence testing of medicines undergoing WHO prequalification (11), since that product’s quality, safety and efficacy have been fully assessed and documented in premarketing studies and post-marketing monitoring schemes. The comparator product can be swallowed whole, or crushed or chewed

and swallowed with water. Existing pharmacopoeial dissolution test conditions for albendazole tablets were taken as a starting point for the WHO investigations. The volume and composition of the dissolution medium were retained; but a higher rotation speed was selected to compensate for the non-disintegrating character of the dosage form.

The final test conditions (Box 2) were found to be discriminative, meaning that the modified test is suitable for comparing and evaluating the *in vitro* release properties of albendazole chewable tablets on the market.

### Adoption process

The procedure for developing monographs for *The International Pharmacopoeia* (12) is designed to ensure wide consultation and transparency, providing stakeholders and interested parties with the opportunity to submit comments on draft documents.

The draft revision of the monograph on albendazole chewable tablets, including the new dissolution test, was therefore

sent out for public consultation in June 2014 and posted on the WHO website (13) with an invitation to provide comments. Thereafter it was submitted, together with a compilation of all comments received, to the Expert Committee on Specifications for Pharmaceutical Products in October 2014. The Committee carefully reviewed the comments and adopted the revised monograph, including the new dissolution test (14). The revised monograph on albendazole chewable tablets is available in the Fifth Edition of *The International Pharmacopoeia* (15).

### References

- 1 WHO Media Centre. Lymphatic filariasis. Fact sheet N° 102. Updated May 2015 [web page].
- 2 WHO Media Centre. Soil-transmitted helminth infections. Fact sheet N° 366. Updated May 2015 [web page].
- 3 ICH Harmonised Tripartite Guideline. Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances. Q6A. Step 4 version. ICH: 1999.

#### Box 2. *The International Pharmacopoeia*\*:

##### Dissolution test requirements for albendazole chewable tablets

Carry out the test as described under Section 5.5 Dissolution test for solid oral dosage forms using 900 mL of hydrochloric acid (~3.65 g/L) TS as the dissolution medium and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 15 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature. Transfer 1.0 mL of the clear filtrate to a 50 mL volumetric flask and dilute to volume with sodium hydroxide (0.1 mol/L) VS. Measure the absorbance (1.6) of a 1 cm layer of the resulting solution at the maximum at about 308 nm, using sodium hydroxide (0.1 mol/L) VS as the blank.

For each of the six tablets tested calculate the total amount of albendazole ( $C_{12}H_{15}N_3O_2S$ ) in the medium using the absorptivity value of 74.2 ( $A_{1cm}^{1\%} = 742$ ). The amount in solution for each tablet is not less than 80% (Q) of the amount declared on the label.

\* *The International Pharmacopoeia* is available on CD and online at <http://apps.who.int/phint/en/p/about/>

- 
- 4 Lindenberg, M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. *Eur J Pharm Biopharm.* 2004 Sep;58(2):265-78.
  - 5 WHO. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. Annex 8. In: WHO Technical Report Series, No. 937. Geneva, Switzerland: 2006
  - 6 Chewable tablets: time to reassess a "neglected" dosage form? WHO Drug Information 2011;25(3):223-7.
  - 7 Suleman S, Zeleke G, Deti H *et al.* Quality of Medicines Commonly Used in the Treatment of Soil Transmitted Helminths and Giardia in Ethiopia: A Nationwide Survey. *PLoS Negl Trop Dis.* 2014 Dec; 8(12): e3345. doi: 10.1371/journal.pntd.0003345.
  - 8 Albonico M, Mathema P, Montresor A *et al.* Comparative study of the quality and efficacy of originator and generic albendazole for mass treatment of soil-transmitted nematode infections in Nepal. *Trans R Soc Trop Med Hyg.* 2007 May;101(5):454-60. Epub 2006 Nov 28.
  - 9 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. Revision 1, March 2003.
  - 10 Brown CK, Friedel HD, Barker AR *et al.* FIP/AAPS Joint Workshop Report: Dissolution/In Vitro Release Testing of Novel/Special Dosage Forms. *Indian J Pharm Sci.* 2011 May-Jun; 73(3): 338–53.
  - 11 WHO Prequalification of Medicines Programme. Recommended comparator products: Neglected Tropical Diseases. Guidance Document, 25 August 2015.
  - 12 WHO. Procedure for the development of monographs and other texts for The International Pharmacopoeia. Annex 1. In: WHO Technical Report Series, No. 992. Geneva, Switzerland: 2015.
  - 13 WHO. Essential medicines and health products. Current projects [web page]. [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/)
  - 14 WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report. WHO Technical Report Series, No. 992. Geneva, Switzerland: 2015.
  - 15 WHO. *The International Pharmacopoeia.* Fifth Edition. Geneva, Switzerland: 2015. Available free of charge at: <http://apps.who.int/phint/en/p/about/>
-

# Quality of medicines

## The WHO CPP Scheme in today's regulatory environment – is it time for change?

**Is the fundamental purpose of providing a Certificate of Pharmaceutical Product (CPP) to assist worldwide patient access to novel medicines still true today?**

### Background

The WHO Certification Scheme for Certificates of Pharmaceutical Products (CPP) is an international voluntary agreement to provide assurance to countries participating in the Scheme about the quality of pharmaceutical products moving in international commerce.

The Scheme was originally endorsed in 1969 as a powerful instrument to assist national regulatory authorities in sharing information and avoiding duplication. This key principle still holds true.

However, since 1997 the Scheme has not changed despite dramatic changes in the regulatory environment within both the issuing and recipient CPP markets. In this article we examine the Scheme as it is used today and ask: is it time for change?

The CPP Network of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) has been collecting experience of how the Scheme operates and influences patient access to medicines. The key observations and recommendations of the Network are described in this article.

---

*The WHO Certification Scheme was originally endorsed by the World Health Assembly in 1969 and has been revised several times, with each revision being endorsed by the World Health Assembly. To enable the continued adaptation of Scheme's use in a rapidly changing environment without the need for intervention by the World Health Assembly, a Questions and Answers (Q & A) document was prepared in 2010 and published as a working document<sup>1</sup>.*

*In 2014 the Expert Committee on Specifications for Pharmaceutical Preparations recommended that the Q & A document should be updated. The CPP Network team of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) proposed a revised document, which was adopted by the Committee in October 2015 based on the usual public consultation process<sup>2</sup> and is planned to be published in the next issue of WHO Drug Information. The article shown below reflects the thoughts of the IFPMA CPP Network team about the current use of the CPP Scheme.*

<sup>1</sup> *WHO Certification Scheme: questions and answers. WHO Drug Information 2011; 25(2):113-121. (Also available as: Working Document QAS 10.374, May 2010.)*

<sup>2</sup> *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce: Questions and answers (Q & A). Proposal for revision. Working document QAS/15.623, June 2015.*

*We thank Marianne Vogt, Heather Hockenhull and the members of the IFPMA CPP Network for their work on the revision of the CPP Questions and Answers document, and for contributing this article.*

---

***Not all accredited authorities meet the requirements or template stated in the guidelines for the Scheme when CPPs are issued.***

More than 130 countries are member states of the Scheme or acknowledge and accept the Scheme. However, not all the authorities meet the requirements or adhere to the WHO template guidelines. This is problematic and often leads to confusion within the recipient countries when the requirements and template vary dependent on the issuing health authority (HA). This can be avoided if the template guidance is adhered to. To address this issue, we recommend that all issuing HAs use the WHO template, which will also lead to improvements in legalization requests. When the guidance is followed, many recipient HAs do not request additional certification of the CPP.

***The way to apply for a CPP is not harmonized, with each certifying authority having its own system.***

There are a variety of systems and procedures across issuing countries on how to apply for a CPP. In order to achieve more transparency of these processes and lead times, it would be helpful to work towards regional harmonization and a standard electronic submission. Harmonization of CPP applications and of payment approaches or methods should be realistic goals resulting in consistent timelines and efficient planning.

***Some certifying authorities have different interpretations of the CPP Scheme, limiting the issuance of a CPP to products manufactured and exported from the certifying country only.***

Due to differing interpretation of the Scheme across issuing HAs, when a product is not manufactured in and exported from the issuing HA country, a full CPP may not be issued and sometimes no CPP will be issued at all. This can result in a substantial delay in registration and patient access within CPP-dependent markets. In line with the original concept of the WHO Scheme a CPP can be issued as soon as the product is approved, independently of where it is manufactured, released and exported from. Adherence to this principle will then allow for products to be registered within shorter time frames in the recipient markets, allowing patients to access the medicines earlier.

***The good manufacturing practice (GMP) status given in the CPP is not recognized by recipient countries.***

A key principle of the Scheme is to share information and **avoid duplication**. In this important aspect, an additional aim of the Scheme is to certify that the respective facilities and operations conform to GMP as recommended by WHO. WHO clearly discourages the request of a separate GMP certificate since the GMP statement included in the CPP should be acceptable.



***There are inconsistencies in listing the trade name of the product in the recipient country, if different from the certifying country.***

Generally most of the certifying countries allow the trade name of the recipient country on the CPP. However, in some cases the trade name is not part of the formatted template application and therefore cannot be displayed within the CPP. Thus HAs can have difficulty recognizing that the CPP prepared by the issuing country is for the same product as that being registered, renewed or varied within the recipient country. The recommendation is that all issuing HAs have the option to include the trade name of the recipient country within the CPP.

***There is lack of understanding that the CPP reflects the approval status of the certifying country only.***

For CPP-dependent markets the CPP is classified as the key document for a successful submission and eventually approval of a drug product. The content of the CPP is extremely important to the recipient market – in most cases the recipient HA requires that the drug product they will receive mirrors exactly the drug product that has been approved by the certifying HA. However, complexities in modern global sourcing routes do not always allow for a direct match. When various steps of the manufacturing process differ between the recipient and issuing countries, this may result in queries and can cause unnecessary delays in approval. We recommend awareness and educational initiatives to clarify to the recipient HAs that the CPP reflects the approval status in the issuing country only with the information on the basis of which it has been approved.

***The CPP is no longer provided to substitute the full dossier quality safety and efficacy (QSE) review.***

Today many countries require provision of the CPP in addition to carrying out their own QSE review thus increasing the time for approval and patient access to novel medicines. In recent years we have seen rapid changes to the global regulatory landscape; however, in many countries the use of the WHO Certification Scheme has remained largely unchanged for the last 20 years. More countries than ever before receive full dossiers, including the country-specific Module 1 of the Common Technical Document (CTD) containing all the details provided in the CPP, from GMP certificates to worldwide marketing authorization (MA) status. In order to reaffirm the original intention of the CPP i.e. to support countries with “limited drug regulatory capacity”, countries capable of carrying out a full QSE evaluation should be advised to review their regulatory requirements and cease to require a CPP as a mandatory element for approval, unless it is to be used for a priority review thus accelerating patient access to novel medicines.

***CPPs are required in the majority of reference country approval markets as a prerequisite for a regulatory submission rather than being provided just prior to approval.***

CPPs are mostly required as a prerequisite for applications in the full life cycle of the drug product (from MA approval to subsequent renewals and variations), thereby directly impacting the availability of novel drugs for patients in those markets. Furthermore, authorities in these markets are moving from requesting an abbreviated dossier (by

relying on approval in a reference market) to a more complex regulatory framework which includes a full dossier (e.g. ICH CTD) plus the CPP. This situation leads to excessively lengthy submission and approval timelines.

It is recommended that HAs accept abbreviated dossiers when they are requesting CPPs and that CPPs are not a requirement for the initial review cycle but can be provided at a later time.

***Required consulate/embassy legalizations lead to delays in CPP availability.***

The CPP is a legal document that adheres to the principles of WHO which are endorsed by the majority of countries. Consulate legalization is sometimes required, which is beyond the international rules for the exchange of certificates and documents as it does not provide any enhanced evidence of authenticity and does not provide value to the safety of the patients. In addition, required legalizations lead to delays in CPP availability, impacting registration timelines and the availability of new medicines to patients. Where a country requires a CPP prior to the approval of a product, consulate/embassy legalization should not be required since the CPP was issued by the HA in accordance with the adopted WHO requirements.

***Lead times of the certifying authorities can be very long, sometimes several months.***

Experience shows that there are differences in the timelines for issuing of CPPs across national authorities, ranging from days to several months. Lengthy issuing times from certifying authorities,

especially those from source countries of new medicines, increase registration timelines and delay availability of those medicines in CPP-dependent markets. It is recommended that HAs that have successfully implemented shorter issuing timelines share best practices with others where issuing timelines are longer.

In addition, there are no specific review timelines for CPP requests. If there is an issue with the application, the applicant is not informed until many weeks after the initial application. Opportunity for the applicant to discuss the submission with the issuing HA during the process would benefit both the HA and the applicant and allow for any corrections or updates to be managed efficiently.

***The marketing authorization holder (MAH) stated within the CPP can be registered as the MAH within the recipient country license.***

There has been a growing trend within markets requiring reference country approval to register the MAH listed within the CPP as the MAH within the recipient market. This leads to issues as the MAH can differ depending on the issuing HA's legislative requirements. In addition there is often a requirement within the recipient HA, that the MAH must be from where the product is formulated and/or released. This makes it impossible to provide a CPP that fits the legislative requirements in the recipient country. Is it correct to use the CPP content in this way? This is not aligned with the Scheme's original purpose to ensure QSE of the drug product moving in international commerce, regardless of whether the MAH listed in the CPP formulates and/or releases the drug product. The original purpose of the Scheme should be reflected within the

recipient HA legislative requirements, allowing CPPs to be provided to support regulatory submissions with proof of the QSE of the drug product only.

### Conclusion

In answer to the question, “Is the fundamental purpose of providing a CPP to assist worldwide patient access to novel medicines still true today?” we have the following opinion:

The CPP Scheme is still valid, but not in its current state and only when used to support countries that **do not** have the infrastructure to complete a full dossier quality, safety and efficacy review themselves.

For the Scheme to be successful now and in the future, both recipient and

issuing HAs need to work together with WHO and the pharmaceutical industry to harmonize CPP templates, align legislative requirements of recipient countries, reduce timelines and accept the CPP at a later time within the review cycle.

Whilst doing this we also need to remain focused on the initial fundamental purpose of the Scheme, ensuring its continuous improvement and adaptation as we move forward with advancements within the regulatory environment.

Only once this has been achieved, will the Scheme work again to its full potential, positively impacting patients worldwide independent of their regulatory authorities' resources and capability. ◆

# Safety news

## Restrictions

### **Mirabegron: contraindicated in patients with severe hypertension**

United Kingdom – The marketing authorization holder, in consultation with the MHRA, has informed health professionals of cases of severe hypertension reported in patients taking mirabegron (Betmiga®), including hypertensive crisis associated with cerebrovascular and cardiac events (mainly transient ischaemia attack or stroke). Mirabegron is now contraindicated in patients with severe uncontrolled hypertension with a systolic blood pressure of 180 mm Hg or higher and/or a diastolic blood pressure of 110 mm Hg or higher. Blood pressure should be measured before starting treatment and periodically during treatment, especially in patients with hypertension.

Mirabegron is used in the management of urinary frequency, urgency, and incontinence in overactive bladder syndrome. It is known that mirabegron can increase blood pressure. Health professionals were also reminded of restrictions in the use of mirabegron in patients with renal impairment and in those with hepatic impairment who are also taking strong inhibitors of cytochrome P450 3A such as itraconazole, ketoconazole, ritonavir, or clarithromycin, as this will lead to increased exposure (area under the curve, AUC) of mirabegron.

► MHRA. Drug Safety Update vol 9 issue 3 October 2015: 1.

## Safety warnings

### **Proton pump inhibitors: subacute cutaneous lupus erythematosus**

United Kingdom – The MHRA has warned that proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE), especially in sun-exposed areas of the skin.

Health professionals should suspect SCLE in patients treated with a proton pump inhibitor who develop such lesions and who report arthralgia. Treatment discontinuation should be considered unless it is imperative for a serious acid-related condition. In most cases, symptoms resolve on PPI withdrawal. If there are no signs of remission after a few weeks or months, treatment with topical or systemic steroids may be necessary.

► [Drug Safety Update vol 9 issue 2 September 2015: 1.](#)

### **Antiviral combinations for hepatitis C: liver injury**

United States of America – The FDA has warned about the risk of potentially serious liver injury in patients taking one of two antiviral fixed-dose combination products used to treat chronic hepatitis C: dasabuvir, ombitasvir, paritaprevir, and ritonavir (Viekira Pak®) and ombitasvir, paritaprevir, and ritonavir (Technivie®). Information about this safety risk has been added to the product information for the two medicines.

Technivie® is FDA-approved for use in patients with genotype 4 chronic hepatitis

C virus infection without cirrhosis, while Viekira Pak® is FDA-approved for use in patients with genotype 1 chronic hepatitis C infection including those with compensated cirrhosis. Serious outcomes were reported mostly in patients taking Viekira Pak® who had evidence of advanced cirrhosis before starting treatment with the drug. (1)

Canada – In response to new international safety information about serious cases of liver injury, Health Canada has recommended updates to product information for the fixed-dose combination of ombitasvir/paritaprevir/ritonavir and dasabuvir (Holkira Pak®) and the fixed-dose combination of ombitasvir/paritaprevir/ritonavir (Technivie®). (2)

► (1) [FDA Drug safety communication](#), 22 October 2015.

(2) [Health Canada Advisory](#), 10 November 2015.

### **Daclatasvir hydrochloride and asunaprevir: interstitial pneumonia**

Japan – The PMDA has requested that product information for daclatasvir hydrochloride (Daklinza®) and asunaprevir (Sunvepra®) should be updated to include information about the risk of interstitial pneumonia in patients treated with a combination of the two medicines. This follows 11 cases reported in Japan in the last three years, including four where causality could not be ruled out.

► [PMDA Summary of investigation results and Revision of Precautions](#), 20 October 2015.

### **Vemurafenib: potentiation of radiation toxicity**

United Kingdom – The MHRA has alerted prescribers to the risk of potentiation of radiation toxicity in patients treated with radiation before, during, or following treatment with vemurafenib (Zelboraf®). Vemurafenib should be used with caution in such patients.

The risk was identified in a review of worldwide data by EU medicines regulators. Severe cases of radiation-related injuries, including some with fatal outcome, have been reported. In the majority of cases, patients received radiotherapy regimens greater than or equal to 2 Gy/day. The events included radiation recall and radiation sensitization. Most cases were cutaneous in nature but some cases involved visceral organs.

► [Drug Safety Update Vol 9 issue 4](#), November 2015: 2.

### **Crizotinib: heart failure**

United Kingdom – The MHRA has warned health professionals about the risk of severe and potentially fatal cardiac failure in patients treated with crizotinib (Xalkori®) identified in a review by European medicines regulators.

Health professionals should monitor all patients for signs and symptoms of heart failure, including dyspnoea, oedema, or rapid weight gain from fluid retention. A dose reduction, treatment interruption or treatment discontinuation should be considered if any of these symptoms occur.

► [Drug Safety Update vol 9 issue 3](#), November 2015: 1.

**Fingolimod: skin cancer**

Canada – Health Canada has approved updates to the product information for the multiple sclerosis drug fingolimod (Gilenya®) to warn about two specific risks associated with the medicine's action on the immune system.

A Health Canada safety review found that fingolimod may increase the risk of cancers, particularly of the skin. Patients and health professionals should be vigilant for symptoms of skin cancer.

Information on the risk of progressive multifocal leukoencephalopathy (PML), as reported in the EU and the U.S. earlier this year, was also added. The risk of lymphoma and of infections was already mentioned in the Canadian monograph.

► [Health Canada Advisory, 30 September 2015.](#)

**Aripiprazole: impulse control disorders**

Canada – Health Canada has approved updates to the product information of aripiprazole (Abilify®) to include a warning about an increased risk of impulsive behaviours of pathological gambling and hypersexuality. (1)

Aripiprazole tablets are authorized to treat a serious type of bipolar disorder, schizophrenia and related severe psychotic disorders and major depressive disorder in adults when used in combination with other drugs. The solution for injection is used for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate. A long-acting product (Aristada®, Abilify Maintena®) – a prolonged-release suspension for injection – is used for

maintenance treatment of schizophrenia in adults.

► (1) [Health Canada Advisory, 2 November 2015.](#)

**Sodium polystyrene sulfonate: separate dosing to prevent interactions**

United States of America – The FDA has informed health professionals that additional studies are being required for the potassium-lowering medicine sodium polystyrene sulfonate (Kayexalate® and generic brands), to investigate its possible interaction with other drugs. Similarly to the recently licenced drug patiomer (Veltassa®), sodium polystyrene sulfonate might bind to other medications, potentially decreasing their effects. To reduce this potential risk, prescribers and patients should consider separating dosing of sodium polystyrene sulfate from that of any other oral medications – both prescription and non-prescription drugs – by at least six hours. Health care professionals should monitor blood levels or clinical response to the other medications when appropriate.

► [FDA Drug safety communication, 22 October 2015.](#)

**Iodine-containing contrast agents: hypoactive thyroid in infants**

United States of America – The FDA has advised that rare cases of underactive thyroid have been reported in infants younger than 4 months following the use of contrast media containing iodine for X-rays and other medical imaging procedures. In all of the reported cases, the infants were either premature or had other serious underlying medical conditions. Available evidence suggests

that this is a rare effect that usually resolves without treatment or lasting effects. Manufacturers of affected products have been required to conduct a study to investigate this safety issue further.

Product information for all iodinated contrast media is being updated to include information about these cases. The FDA will continue to evaluate this issue.

- [FDA Drug safety communication](#), 17 November 2015.

### Known risks

#### **Magnesium oxide: hypermagnesaemia in older patients**

Japan – The PMDA has warned that numerous cases of hypermagnesaemia have been reported in geriatric patients treated with magnesium oxide granules or tablets, with some serious outcomes even if the renal function was normal or if the dosage was below the recommended dose. In many cases, the hypermagnesaemia was only detected when serious outcomes such as loss of consciousness occurred.

Product information has been updated with advice that the medicine should be used with caution in geriatrics. Patients should be instructed to stop taking the medication and seek medical help immediately if they experience vomiting, bradycardia, muscular weakness, or somnolence. Patients should be carefully monitored with periodic measurement of serum magnesium concentration. For over-the-counter laxatives containing magnesium oxide, advice has been added to the package insert that elderly persons

should consult a health professional before taking the product.

- [PMDA Summary of investigation results and Revisions of precautions](#) for prescription products, 20 October 2015.

[PMDA Summary of investigation results and Revisions of precautions](#) for over-the-counter laxatives, 20 October 2015

#### **Canagliflozin: decreased bone mineral density**

United States of America – Based on updated information from several clinical trials the FDA has strengthened its warning about the increased risk of bone fractures in patients treated with the antidiabetic medicine canagliflozin (Invokana®, Invokamet®). Fractures can occur as early as 12 weeks after starting the drug. New information about the risk of decreased bone mineral density has been added to the section on adverse reactions in the product information. Health care professionals should consider factors that contribute to fracture risk before starting patients on canagliflozin.

The FDA is evaluating the risk of fractures with other SGLT2 inhibitors registered in the U.S., including dapagliflozin (Farxiga®, Xigduo XR®) and empagliflozin (Jardiance®, Glyxambi®, Synjardy®).

- [FDA Drug safety announcement](#), 10 September 2015.

#### **Mycophenolate: avoid exposure in pregnancy**

European Union – The EMA has strengthened its warnings about exposure of pregnant women to the transplant medicine mycophenolate (CellCept® and other brand names) either by treatment with the medicine or through unprotected sex with a man taking the medicine. A



routine re-assessment of the benefits and safety of mycophenolate has provided updated evidence on the significant risk of birth defects and spontaneous abortions.

Pregnant women should only be exposed to mycophenolate if there is no suitable alternative to prevent transplant rejection. Mycophenolate can persist in blood for six weeks after treatment, and in sperm for 90 days after treatment. Updated product information will emphasize the need for contraception with two effective methods during and after treatment, pregnancy testing as appropriate, and the need to avoid donating blood or sperm during and after treatment with mycophenolate.

► [EMA Press release, 23 October 2015.](#)

### **Ceftriaxone: acute generalised exanthematous pustulosis**

Japan – The PMDA has requested updates to the product information to ceftriaxone sodium hydrate to include the risk of acute generalised exanthematous pustulosis. This follows reports of this adverse event in patients treated with ceftriaxone sodium hydrate both in Japan and overseas. A warning about this risk is included in the product information for ceftriaxone-containing medicines approved in the European Union.

► [PMDA Summary of investigation results and Revisions of precautions, 20 October 2015.](#)

### **Roxithromycin: pseudo-membranous colitis, cardiac effects**

Japan – The PMDA has required updates to the product information for roxithromycin-containing medicines to warn about the risks of pseudomembranous colitis and of QT interval prolongation and ventricular

tachycardia, including torsade de pointes. This follows reports of these events in Japan and elsewhere. Approved product information in the European Union includes warnings about these effects.

► [PMDA Summary of investigation results and Revision of precautions, 20 October 2015.](#)

### **Strontium: cardiovascular risks**

Canada – Health Canada has implemented strengthened warnings on cardiovascular risks associated with products containing strontium citrate, strontium gluconate or strontium lactate with a daily dose of strontium between 4 mg and 682 mg, which are used to help support bone mineral density. These products are now limited to users who have no history of heart disease, circulatory problems or blood clots, or risk factors for these conditions. A healthcare professional should be consulted if the product is used longer than six months.

This follows a Health Canada review undertaken in light of findings in Europe that led to restrictions for strontium ranelate at strontium doses of 680 mg/day. A Health Canada review of strontium ranelate at daily doses below 680 mg/and of non-ranelate forms of strontium did not lead to firm conclusions. However, Health Canada is using a precautionary approach and considers that strontium-containing medicines may potentially have cardiovascular side effects in people who are already at risk.

► [Health Canada advisory, 22 October 2015.](#)

### **Clozapine: severe neutropenia**

United States of America – The FDA has approved changes to the requirements for monitoring, prescribing, dispensing and receiving

the schizophrenia medicine clozapine, to address continuing safety concerns about severe neutropenia.

A new, shared risk evaluation and mitigation strategy (REMS), the so-called Clozapine REMS Program, replaces the separate clozapine registries maintained by individual manufacturers. In addition, neutropenia should now be monitored by the absolute neutrophil count (ANC) only, rather than in conjunction with the white blood cell count. Patients with benign ethnic neutropenia (BEN) are now also eligible for clozapine treatment. The ANC below which treatment should be interrupted in case of suspected clozapine-induced neutropenia has been lowered to 1 000 cells/mm<sup>3</sup>, and to 500 cells/mm<sup>3</sup> for patients with BEN.

► [FDA Drug safety communication, 15 September 2015.](#)

### **Dimethyl fumarate and other fumarate-containing medicines: new monitoring measures**

European Union –The EMA has issued advice in order to minimize the risk of progressive multifocal leukoencephalopathy (PML) in patients treated with the multiple sclerosis medicine dimethyl fumarate (Tecfidera®). This follows reports of PML in patients that were not treated with any other medicines that may increase the risk of PML.

According to the new recommendations a complete blood count should be performed before starting treatment and every three months thereafter. Additionally, a baseline MRI should be provided. If during treatment the treatment lymphocyte counts drop to very low levels for more than six months, health professionals should consider stopping treatment. If

treatment is continued, patients should be closely monitored.

Related recommendations have been issued for two fumarate-containing medicines used to treat psoriasis (Fumaderm® and Psorinovo®).

► [EMA Press release, 23 October 2015.](#)

### **Unchanged recommendations**

#### **Clopidogrel: no increased risk of death**

United States of America – The FDA has determined that long-term use of the antiplatelet drug clopidogrel (Plavix®) does not increase or decrease overall risk of death in patients with, or at risk for, heart disease. Neither did a review of clinical trials suggest that clopidogrel increases the risk of cancer or death from cancer. The FDA's recommendations remain unchanged. Health care professionals should consider the benefits and risks of available antiplatelet medicines before starting treatment.

► [FDA Drug safety announcement, 6 November 2015.](#)

#### **Human papillomavirus vaccines: benefits outweigh risks**

European Union – The EMA has completed a detailed scientific review of the evidence surrounding reports of two syndromes, complex regional pain syndrome and postural orthostatic tachycardia syndrome in young women given human papillomavirus (HPV) vaccines. This review concluded that the evidence does not support a causal link between the vaccines (Cervarix®, Gardasil/Silgard® and Gardasil-9®) and development of either of the two syndromes.

More than 80 million girls and women worldwide have received HPV vaccines to protect them from cervical cancer and various other cancers and conditions caused by HPV. The EMA has confirmed that the benefits of these vaccines therefore continue to outweigh their risks, and that no changes to the product information are necessary.

► [EMA Press release, 20 November 2015.](#)

### Entacapone: no clear evidence of cardiovascular events

United States of America – Following concerns about a possible increased risk of heart attacks, stroke or other cardiovascular events associated with entacapone (Comtan®) and with the combination of entacapone, carbidopa and levodopa (Stalevo®), an FDA review has found no clear evidence of such a risk associated with the use of the two medicines.

Entacapone-containing products are used to treat symptoms of Parkinson's disease. In view of cardiovascular-related findings in clinical trials involving Stalevo®, the FDA had required the manufacturer to conduct an additional

study, and had reviewed findings from this and another published study.

► [FDA Drug safety communication, 26 October 2015.](#)

### Removal of class warnings

#### HIV medicines: class warnings about lipodystrophy and lactic acidosis removed

European Union – HIV medicines will no longer require a warning concerning lipodystrophy, i.e. fat redistribution, in their product information, and a number of nucleoside and nucleotide analogues will no longer require a warning about lactic acidosis.

Recent analyses show that only certain medicines cause fat changes, and that these fat changes concern lipoatrophy, i.e. the loss of subcutaneous fat. A specific warning related to lipoatrophy will remain in the product information for medicines containing zidovudine, stavudine and didanosine, and these medicines will also retain the lactic acidosis warning in line with current evidence.

► [EMA Press release, 23 October 2015.](#)

### Safety reviews started

Medicine	Use	Concerns	Reviewing authority reference
Fusafungine-containing nasal and mouth sprays	Treatment of upper airway infection	Serious allergic reactions including anaphylactic reactions	► <a href="#">EMA. Start of review of nasal and mouth sprays containing Fusafungine, 11 September 2015.</a>
Tramadol	Analgesic, not FDA-approved for use in children but being used off-label	Rare but serious risk of slow or difficult breathing in children aged 17 years and younger	► <a href="#">FDA Drug safety communication, 21 September 2015.</a>

**Packaging****Improved packaging for dementia treatments**

United Kingdom – The MHRA is working with the pharmaceutical industry to optimize the presentation of medicines for Alzheimer's disease. To help patients retain independence in taking their medicines, the days of the week will be indicated clearly on the blister packs. The change is expected to help improve patient confidence, safety and treatment outcomes. The improved packaging will be introduced from June 2016.

► [MHRA Press release, 3 November 2015.](#)

**Medicines quality****Apotex: Canada import ban lifted, product re-testing imposed**

Canada – Health Canada has lifted the import restrictions imposed in September 2014 on products from the Indian companies Apotex Pharmachem India Pvt. Ltd. (APIPL) and Apotex Research Private Limited (ARPL), and has imposed re-testing of products from the two sites at an Apotex good manufacturing practices-compliant facility in Canada and reporting of any deficient results. In September 2015, Health Canada inspectors started being present in Apotex's Canadian facility to inspect the operations and the testing of the products from India.

In June 2015, Health Canada had inspected the corrective measures implemented at the Indian two sites and found that they have progressed in a satisfactory manner. Apotex Inc. has been requested to provide regular progress updates on the full and sustainable implementation of corrective actions at full production. Health Canada plans to re-inspect the sites in early 2016.

► [Health Canada Advisory, 1 September 2015.](#)

**Dibotermín alfa-containing implant kit: suspended in Europe**

European Union – The EMA has recommended the suspension of a kit for implant containing a powder, solvent and absorbable collagen sponge (Inductos®) due to manufacturing-related quality issues. This follows a review triggered by observations during inspection of the manufacturing site, located in the United States, by Dutch and Spanish authorities. Although there is no indication of risk to patients directly linked to the inspection findings, the suspension will remain in force until the issues are addressed.

The kit contains dibotermín alfa, a protein that helps with the formation of new bone tissue that grows into the sponge, which is gradually degraded by the body. Alternative treatments are available in the European Union.

► [EMA Press release, 23 October 2015.](#)

**Falsified product alert**

The following text is reproduced from the WHO Medical Product Alert No. 5/2015.

**Falsified emergency contraceptive circulating in East Africa**

This Medical Product Alert relates to the confirmed circulation of falsified versions of Postinor-2 (Levonorgestrel) in East Africa.

Postinor-2 is a widely used emergency contraceptive that should contain 0.75mg of levonorgestrel. The genuine product is manufactured by Gedeon Richter.

In August 2015, the Uganda National Drug Authority notified WHO of the seizure of falsified Postinor-2 discovered in Kampala, Uganda. All packs reported bear the same batch number and expiry/manufacturing dates.

The details of the product are as follows:

- Product Name: **Postinor-2**
- Batch Number: **T38012**
- Manufacturing Date: **08 2013**
- Expiry Date: **08 2018**

**There is a non-useable, white “scratch area” on the reverse side of the pack.** The packaging is in English, French and Spanish languages.

The batch number and manufacturing/expiry dates relate to a genuine batch of Postinor-2. Laboratory analysis has shown that the product contains zero active pharmaceutical ingredient. Furthermore, the manufacturers of genuine Postinor-2 have confirmed the packaging is falsified.

If you are in possession of the same batch of Postinor-2 shown in the below photograph and with a non-useable white “scratch area” on the reverse side of the pack please do not use, contact a Pharmacist or a Doctor as soon as possible for advice and report the incident to your National Medicines Regulatory Authority.

If you think you have taken this product, please seek medical advice immediately.

If you have any information concerning the supply of this product please contact [rapidalert@who.int](mailto:rapidalert@who.int)

► [WHO. Medical Product Alert N° 5/2015. 18 November 2015 \(includes photograph\).](#)

# Regulatory news

## Pre-market assessment

### Accelerated access pathways in Europe

European Union – The EMA has sought public comments on its revised guidelines on the implementation of accelerated assessment and conditional marketing authorization (1). The revised guidelines provide more details on how to justify fulfilment of a major public health interest and on the importance of planning and early dialogue. More recently, EMA has also launched a public consultation on its new proposed PRIME scheme to optimize development of priority medicines and facilitate patients' access (2).

In their public input to the former consultation process (3), Health Action International (HAI), the International Society of Drug Bulletins (ISDB) and the Medicines in Europe Forum (MIEF) have emphasized the importance of concrete evidence demonstrating a new drug's safety and therapeutic advance, of enforcing compliance with post-market obligations, and of ensuring transparency of accelerated decision-making by making assessment reports and expert statements publicly available. The three organizations have further published a joint briefing paper, in which they caution against adaptive pathways becoming the rule even when no genuine public health need exists (4).

► (1) [EMA News, 27 July 2015.](#)

(2) [EMA News, 26 October 2015.](#)

(3) [HAI, ISDB, MIEF. Joint response to EMA public consultation. 30 September 2015.](#)

(4) "Adaptive licensing" or "adaptive pathways": Deregulation under the guise of earlier access. Joint briefing paper. Brussels: HAI, ISDB, MIEF; 16 October 2015.

## Regulatory systems

### New Zealand working on new regulatory regime

New Zealand – The New Zealand Government is working on a new and comprehensive national regulatory regime to regulate therapeutic products, i.e. the wide range products intended to be used in or on human beings for a therapeutic purpose including medical devices and cell and tissue therapies, which are currently not fully regulated in New Zealand. This follows the cessation of the Australia New Zealand Therapeutic Products Agency (ANZTPA) project. The intention is for a Bill to be introduced to Parliament in 2016.

► New Zealand Ministry of Health. [Web page, updated 16 September 2015.](#)

## Post-marketing control

### EMA initiative to improve patient registries

European Union – The EMA has launched an initiative aimed at making better use of patient registries as a source of high-quality post-authorization data on medicines in clinical use.

Registries collect information over time on patients who are diagnosed with a particular disease or who receive particular treatments. Some registries are kept by pharmaceutical companies as a

regulatory requirement, while others are operated at national or international levels for example by physicians' associations or national agencies. Existing registries are not sufficiently coordinated or harmonized, leading to inefficiencies.

The initiative is managed by a cross-committee task force and includes two components: a collaborative strategy and a pilot phase. The strategy aims to facilitate the interactions between coordinators of registries, regulators and pharmaceutical companies, and to identify methodological components for newly established registries to ensure that high quality and relevant data are collected. The pilot phase aims to test whether the strategy meets stakeholders' needs on the basis of real-life examples. It is anticipated to last for two years. Participation will be determined on a case-by-case basis by the cross-committee task force.

► [EMA News, 12 October 2015.](#)

## Collaboration and harmonization

### ICH announces organizational changes

Geneva – The International Council for Harmonisation (ICH), formerly known as the International Conference on Harmonisation, has announced organizational reforms to equip it better to face the challenges of global pharmaceutical development and regulation.

The reforms aim to expand ICH beyond the current membership to make it a truly global initiative. Regulators around the world will be invited to join counterparts from Europe, Japan, USA, Canada and Switzerland as ICH regulatory members. This is matched by the possibility of wider inclusion of global industry sectors

affected by ICH harmonization. ICH aims to be the leading platform for global pharmaceutical regulatory harmonisation, bringing together in a transparent manner all key regulatory authorities and industry stakeholders. The ICH operating structure will be an association under Swiss law, which establishes the new Assembly as the overarching governing body.

► ICH Press release, 26 October 2015.

### China and WHO collaborate on medicines quality

Geneva – The long-standing collaboration between China and WHO to promote access to good quality pharmaceuticals was formalized in September 2015 when the Chinese Food and Drug Authority (CFDA) and WHO signed a 'cooperation plan' at WHO headquarters. The plan sets out a comprehensive package of measures that China will undertake with WHO's technical assistance, specifically to improve the quality of generic medicines, create a more science based and efficient review and approval system, reduce drug submission backlogs and promote transparency of operations.

► WHO Essential medicines and health products. [China – growing potential to supply affordable quality medicines](#) [web page].

### Meeting of World Pharmacopoeias held in China

China – The 6<sup>th</sup> International Meeting of World Pharmacopoeias was co-hosted by the Chinese Pharmacopoeia (ChP) and WHO in Suzhou, China, on 21–22 September 2015. Achieving global standards to expand access to quality medicines globally was key to the discussions of the meeting, which was



held in connection with the 2015 ChP Annual Scientific Symposium. Twelve pharmacopoeias from all around the globe attended, including the European Pharmacopoeia on behalf of its 38 signatories.

An important output of this international meeting was the finalization of the first-ever guideline on Good Pharmacopoeial practices, based on feedback received during wide global consultation, for presentation to the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The Committee's adoption of this guideline at its 50<sup>th</sup> meeting in October 2015 (see also page 481) marks a significant step forward in setting globally unified principles for creating quality standards for medicines.

► WHO Essential medicines and health products. [Meeting of World Pharmacopoeias in China benefits the world's](#) [web page].

### Regulators of United Kingdom and India sign agreement

New Delhi – The Medicines and Healthcare products Regulatory Agency (MHRA) and the Central Drugs Standard Control Organisation (CDSCO) under the Ministry of Health and Family Welfare of the Republic of India have signed a Memorandum of Understanding (MOU). The agreement aims to facilitate regulatory information exchange and technical cooperation of mutual benefit, helping to protect the health and public safety in the two countries.

In 2014, MHRA carried out 125 inspections in non-EU countries, 49 of which were in India. Approximately 25% of

the medicines sold in the United Kingdom are made in India. The agreement is part of a concerted effort to promote good manufacturing practices throughout the pharmaceutical industry, benefitting the global public. Similar agreements are already in place between MHRA and counterpart bodies in China and America.

► [MHRA Press release, 5 October 2015.](#)

### EMA and WHO share non-public information

European Union – The European Commission, EMA and WHO have concluded a working arrangement that allows timely sharing of non-public information on the safety, quality and efficacy of medicines already authorized or under review in the European Union (EU), or prequalified or under review by WHO. This cooperation started on 1<sup>st</sup> September 2015.

The arrangement will make it easier and quicker to communicate and take action to protect public health. Examples of information that may be shared include:

- pharmacovigilance data, particularly urgent information on EU-originating or non-EU originating adverse reactions;
- information on applications for scientific advice, orphan medicine designation, marketing authorization, post-authorization activities of significant public health interest, and applications for agreement of paediatric investigation plans; and
- data and reports related to inspections, manufacturing facilities and clinical research activities.

► [EMA News, 22 September 2015.](#)

**Approved****Insulin degludec & insulin aspart for diabetes mellitus****Product name:** Ryzodeg 70/30®**Dosage form:** Injection**Class:** Combination of a long-acting insulin analog (insulin degludec) and a rapid-acting human insulin analog (insulin aspart): *ATC code:* A10AD06**Approval:** FDA**Use:** Improvement of glycaemic control in adults with type 1 and 2 diabetes mellitus**Benefits:** Additional treatment option for diabetes; ability to reduce HbA1c equivalent to reductions achieved with FDA-approved long-acting or pre-mixed insulin products.**Safety information:** The product should not be used in patients with diabetic ketoacidosis. Like other insulins, it may cause severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock, as well as hypoglycaemia which can be life-threatening.**Notes:** The FDA has also approved insulin degludec (Tresiba®) which was approved by EMA in 2013.► [FDA News release, 25 September 2015.](#)**Efmoroctocog alfa for haemophilia A****Product name:** Elocta®**Dosage form:** Powder and solvent for solution for injection**Class:** Antihæmorrhagic (*ATC code:* B02)**Approval:** EMA (orphan designation)**Use:** Treatment and prophylaxis of bleeding in patients with haemophilia A**Benefits:** provide adequate prophylaxis in terms of annualised bleeding**Benefits:** Ability to provide adequate prophylaxis in terms of annualised bleeding rate, to control bleeding on demand and to provide haemostatic efficacy for surgical procedures.**Safety information:** Hypersensitivity reactions have been reported rarely.► [EMA/CHMP Summary of opinion, 24 September 2015.](#)**Modified antihæmophilic factor (recombinant)****Product name:** Adynovate®**Dosage form:** Lyophilized powder for solution for intravenous injection.**Class:** Blood coagulation factor**Approval:** FDA**Use:** On-demand treatment and control of bleeding episodes for prophylaxis in patients with hæmophilia A.**Benefits:** This PEGylated product potentially requires less frequent injections than unmodified antihæmophilic factor.► [FDA News release, 13 November 2015.](#)**Coagulation Factor X (human) for hereditary Factor X deficiency****Product name:** Coagadex®**Class:** Blood coagulation factor;  
*ATC code:* B02BD13**Approval:** FDA (orphan designation)**Use:** Treatment of individuals aged 12 and older with hereditary Factor X deficiency for on-demand treatment and control of bleeding episodes, and for perioperative management of bleeding in patients with mild hereditary Factor X deficiency.**Benefits:** The availability of a purified Factor X concentrate increases treatment options for patients with this rare hereditary condition.► [FDA News release, 20 October 2015.](#)**Patiromer for hyperkalaemia****Product name:** Veltassa®**Dosage form:** Powder for oral suspension**Class:** Potassium binder; polymer**Approval:** FDA**Use:** Treatment of hyperkalaemia. Not appropriate for rapid correction of severe

## Approved

hyperkalaemia as lowering of serum potassium may take hours to days.

**Benefits:** In clinical trials, patiromer was effective in lowering potassium levels in hyperkalaemic participants with chronic kidney disease taking one or more renin-angiotensin-aldosterone system inhibitors.

**Safety information:** Patiromer binds many other orally administered drugs, which could decrease their absorption and reduce their effects. It should be taken at least six hours before or after any other orally administered medication.

► [FDA News release, 21 October 2015.](#)

### Elvitegravir & cobicistat & emtricitabine & tenofovir alafenamide for HIV infection

**Product name:** Genvoya®

**Dosage form:** Film-coated tablet

**Class:** Antiretroviral, fixed-dose combination;  
ATC code: J05AR18

**Approval:** EMA

**Use:** Treatment of adults and adolescents infected with human immunodeficiency virus 1 without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir

**Benefits:** Potent antiretroviral response in a once daily, single pill regimen; lower impact on renal safety and bone mineral density than tenofovir disoproxil.

► [EMA/CHMP Summary of opinion, 24 September 2015.](#)

### Uridine triacetate for a rare hereditary metabolic disorder

**Product name:** Xuriden®

**Dosage form:** Oral granules

**Class:** Nucleoside

**Approval:** FDA (orphan drug designation)

**Use:** Treatment of hereditary orotic aciduria, a very rare metabolic disorder that prevents the body from synthesizing uridine, a necessary component of ribonucleic acid (RNA). This causes

blood count disorders and urinary tract obstruction due to the formation of orotic acid crystals, resulting in failure to thrive and developmental delays.

**Benefits:** Uridine replacement; stabilisation of the haematologic parameters.

► [FDA News release, 4 September 2015.](#)

### Trifluridine & tipiracil for advanced colorectal cancer

**Product name:** Lonsurf®

**Dosage form:** Tablet

**Class:** combination of a nucleoside metabolic inhibitor (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil);  
ATC code: L01BC59

**Approval:** FDA

**Use:** Treatment of patients with advanced (metastatic) colorectal cancer who have been previously treated with chemotherapy and biological therapy.

**Benefits:** Additional treatment option for metastatic colorectal cancer.

**Safety information:** Risk of severe myelosuppression. Complete blood counts should be obtained before starting each treatment cycle, and patients should be monitored throughout treatment. Women should be advised of potential risks to developing foetuses. Women on treatment with this product should not breastfeed.

► [FDA News release, 22 September 2015.](#)

### Blinatumomab for certain acute lymphoblastic leukaemias

**Product name:** Blincyto®

**Dosage form:** Powder in a vial for preparing a concentrate for solution for infusion, and stabilising solution

**Class:** Bispecific T-cell engager antibody;  
ATC code: L01XC19

**Approval:** EMA (conditional marketing authorization; orphan designation)

**Use:** Treatment of adults with Philadelphia chromosome-negative relapsed or

refractory B-precursor acute lymphoblastic leukaemia.

**Benefits:** Ability to increase the proportion of patients who have complete remission and molecular remission within the first two treatment cycles.

► [EMA CHMP Summary of opinion, 24 September 2015.](#)

### **Necitumumab for advanced squamous non-small cell lung cancer**

**Product name:** Portrazza®

**Dosage form:**

**Class:** monoclonal antibody, EGFR-blocker:  
**ATC code:** L01XC22

**Approval:** FDA

**Use:** Treatment of patients with advanced (metastatic) squamous non-small cell lung cancer who have not previously received medication specifically for this cancer.

**Benefits:** New treatment option for certain patients with squamous cell lung cancer, ability to extend survival.

**Safety information:** The product carries a boxed warning to alert health care providers about serious risks of cardiac arrest and sudden death, as well as hypomagnesaemia with potentially fatal outcomes.

► [FDA News release, 24 November 2015.](#)

### **Cobimetinib for metastatic melanoma**

**Product name:** Cotellic®

**Dosage form:** Film-coated tablets

**Class:** Antineoplastic agent; mitogen-activated protein kinase (MAPK) pathway inhibitor (**ATC code:** L01XE)

**Approval:** EMA, FDA (priority review; orphan drug designation)

**Use:** In combination with vemurafenib, treatment of unresectable or metastatic melanoma in patients with a BRAF V600 mutation

**Benefits:** Longer progression-free survival in melanoma patients with a BRAFV600

mutation, compared with vemurafenib monotherapy.

**Safety information:** May cause severe side effects including cardiomyopathy, rhabdomyolysis, new skin tumours, retinal detachment, liver damage, bleeding and severe skin rash due to photosensitivity. Women taking cobimetinib should use effective contraception.

**Notes:** The product was first approved by [Swissmedic](#) in August 2015.

► [EMA CHMP Summary of opinion, 24 September 2015.](#)

[FDA News release, 10 November 2015.](#)

### **Irinotecan liposome injection for advanced pancreatic cancer**

**Product name:** Onivyde®

**Dosage form:** Liposome injection

**Class:** Antineoplastic agent;  
**ATC code:** L01XX19

**Approval:** FDA (orphan designation; priority review)

**Use:** In combination with fluorouracil and leucovorin, to treat patients with advanced (metastatic) pancreatic cancer who have been previously treated with gemcitabine-based chemotherapy.

**Benefits:** Longer survival period, compared to patients treated with fluorouracil and leucovorin only.

**Safety information:** The medicine carries a Boxed Warning about the risks of severe neutropenia and diarrhoea. Death due to sepsis following neutropenia has been reported in patients treated with irinotecan. The medicine is not FDA-approved for use as a single agent.

► [FDA Press announcement, 22 October 2015.](#)

### **Carfilzomib for a rare type of blood cancer**

**Product name:** Kyprolis®

**Dosage form:** Powder for solution for injection

## Approved

**Class:** Irreversible proteasome inhibitor;  
*ATC code:* L01XX45

**Approval:** EMA (accelerated assessment, orphan designation)

**Use:** In combination with lenalidomide and dexamethasone, treatment of adult patients with multiple myeloma who have received at least one prior therapy.

**Benefits:** More sustained inhibition of targeted proteasome with minimal inhibition of other non-targeted enzymes; longer progression-free interval.

**Safety information:** Serious side effects include blood abnormalities and cardiac events. A follow-up plan was approved to monitor the safety and efficacy of carfilzomib.

► [EMA Press release, 25 September 2015.](#)

**Ixazomib for multiple myeloma**

**Product name:** Ninlaro®

**Dosage form:** Capsule

**Class:** Antineoplastic – first oral proteasome inhibitor; *ATC code:* L01XX50

**Approval:** FDA (orphan drug designation; priority review)

**Use:** In combination lenalidomide and dexamethasone, to treat patients with multiple myeloma who have received at least one prior therapy.

**Benefits:** New oral treatment with ability to slow disease progression when other therapy has failed.

► [FDA News release, 20 November 2015.](#)

**Talimogene laherparepvec for advanced melanoma**

**Product name:** Imlygic®

**Dosage form:** Solution for injection

**Class:** Oncolytic virus derived from HSV-1 (a first-in-class advanced therapy medicinal product)

**Approval:** EMA, FDA

**Use:** Treatment of adults with unresectable melanoma. The product is directly injected into lesions in the skin or lymph nodes.

**Benefits:** Increased durable response rate – defined as disappearance of the tumours or at least 50% reduction of tumours lasting at least six months – compared to treatment with the immune stimulatory protein human GM-CSF. The product has not been shown to improve overall survival or to have an effect on melanoma that has spread to the brain, bone, liver, lungs, or other internal organs.

**Safety information:** This product is a modified live oncolytic herpes virus therapy, therefore herpes virus infection can occur. Given this, the product should not to be used in patients who are immunocompromised, or in pregnant women.

► [EMA Press release, 23 October 2015.](#)

[FDA News release, 27 October 2015.](#)

**Mepolizumab for asthma**

**Product name:** Nucala®

**Dosage form:** Powder for solution for injection

**Class:** Humanised monoclonal antibody targeting human interleukin-5;  
*ATC code:* L04AC06

**Approval:** EMA, FDA

**Use:** Treatment of patients 12 years and older with severe refractory eosinophilic asthma.

**Benefits:** Can reduce the number of asthma exacerbations in patients who either remain uncontrolled on their previous standard of care or who are dependent on systemic corticosteroids.

**Safety information:** Hypersensitivity reactions can occur within hours or days of treatment.

► [EMA/CHMP Summary of opinion, 24 September 2015.](#)

[FDA News release, 4 November 2015.](#)

**Osimertinib for certain non-small cell lung cancers**

**Product name:** Tagrisso®

**Dosage form:** Tablet

**Class:** Third-generation tyrosine kinase inhibitor

**Approval:** FDA (breakthrough therapy designation, priority review and orphan drug designation; accelerated approval. Continued approval for this indication may be contingent upon further confirmatory studies.)

**Use:** Treatment of patients with advanced non-small cell lung cancer whose tumours have the T790M epidermal growth factor receptor (EGFR) mutation and have progressed on or after treatment with other EGFR-blocking therapy.

**Benefits:** Reduction of tumour size was observed in more than half of the patients treated in two clinical trials.

**Safety information:** May cause serious side effects, including inflammation of the lungs and injury to the heart. May cause harm to a developing foetus.

**Notes:** The FDA also approved a companion diagnostic test (cobas EGFR Mutation Test v2) to detect the T790M mutation.

► [FDA News release, 13 November 2015.](#)

### Daratumumab for multiple myeloma

**Product name:** Darzalex®

**Dosage form:** Injection for intravenous use

**Class:** Antineoplastic; human CD38-directed monoclonal antibody

**Approval:** FDA (breakthrough therapy designation, priority review and orphan drug designation; accelerated approval)

**Use:** Treatment of treat patients with multiple myeloma who have received at least three prior treatments.

**Benefits:** Ability to achieve complete or partial reduction in tumour burden.

**Safety information:** Daratumumab may cause serious infusion reactions. Daratumumab may interfere with certain tests that are done by blood banks (such as antibody screening) for patients who need a blood transfusion.

► [FDA News release, 16 November 2015.](#)

### Cariprazine for schizophrenia and bipolar disorder

**Product name:** Vraylar®

**Dosage form:** Capsules

**Class:** Antipsychotic, ATC code: N05AX15

**Approval:** FDA

**Use:** Treatment of schizophrenia and bipolar disorder in adults

**Benefits:** Reduction of symptoms of schizophrenia and bipolar disorder

**Safety information:** As all other FDA-approved products for treatment of schizophrenia and bipolar disorder, the product has a Boxed Warning about an increased risk of death associated with the use of these drugs in older people with dementia-related psychosis. Neither cariprazine nor any other drug in this class is approved to treat such patients.

► [FDA News release, 17 September 2015.](#)

### Pitolisant for narcolepsy

**Product name:** Wakix®

**Dosage form:** Film-coated tablets

**Class:** Antagonist/inverse agonist of the histamine H3 receptor (first-in-class); ATC code: N07XX11

**Approval:** EMA (orphan designation)

**Use:** Treatment of adult patients with narcolepsy with or without cataplexy. Narcolepsy is a rare, long-term sleep disorder which affects the brain's ability to regulate the normal sleep-wake cycle, and may occur with or without cataplexy (sudden severe muscle weakness or loss of muscle control).

**Benefits:** Ability to reduce excessive daytime sleepiness in patients with narcolepsy, and to decrease cataplexy rate.

► [EMA Press release, 20 November 2015.](#)

### Naloxone nasal spray for opioid overdose

**Product name:** Narcan®

**Dosage form:** Nasal spray

**Class:** Antidote; ATC code: V03AB15

## Approved

**Approval:** FDA (fast-track designation, priority review)

**Use:** To reverse the effects of an opioid overdose.

**Benefits:** Easier to deliver than injectable dosage form, with no risk of a contaminated needle stick.

► [FDA News release, 18 November 2015.](#)

**Idarucizumab for reversal of dabigatran anticoagulant effect**

**Product name:** Praxbind®

**Dosage form:** Solution for injection/infusion

**Class:** Humanised monoclonal antibody fragment; ATC code: V03AB

**Approval:** EMA

**Use:** Indicated in adult patients treated with dabigatran etexilate (Pradaxa®) when rapid reversal of the latter's anticoagulant effects is required: (1) for emergency surgery/urgent procedures or (2) In life-threatening or uncontrolled bleeding. For hospital use only.

**Benefits:** Ability to reverse the anticoagulant effect of dabigatran within 5 minutes of administration, enabling clinical emergency management of patients if needed. Does not interfere with routine treatment in case of bleeding or urgent surgery.

► [EMA Press release, 25 September 2015.](#)

**Patiromer for hyperkalaemia**

**Product name:** Veltassa®

**Dosage form:** Powder for oral suspension

**Class:** Potassium binder; polymer

**Approval:** FDA

**Use:** Treatment of hyperkalaemia. Not appropriate for rapid correction of severe hyperkalaemia because lowering of serum potassium may take hours to days.

**Benefits:** In clinical trials, patiromer was effective in lowering potassium levels in

hyperkalaemic participants with chronic kidney disease taking one or more renin-angiotensin-aldosterone system inhibitors.

**Safety information:** Patiromer binds many other orally administered drugs, which could decrease their absorption and reduce their effects. It should be taken at least six hours before or after any other orally administered medication.

► [FDA News release, 21 October 2015.](#)

**EMA Article 58 positive opinion****Pyronaridine-artesunate – paediatric antimalarial formulation**

**Product name:** Pyramax®

**Additional dosage form:** Granules for oral suspension

**Class:** Antimalarial, artemisinin combination therapy

**Approval:** EMA positive opinion under Article 58. This programme allows the EMA to assess and give a scientific opinion in cooperation with the World Health Organization (WHO) for medicines intended exclusively for markets outside the European Union (EU). Through this mechanism, regulators outside the EU can use the CHMP assessment as part of their national authorisation process.

**Newly approved use:** Treatment of malaria caused by *P. falciparum* and *P. vivax* in children and infants weighing 5 kg to less than 20 kg under 20 kg. Restrictions were also removed on repeated courses of treatment in patients and on its use only in areas of low malaria transmission with evidence of artemisinin resistance.

**Note:** This artemisinin combination therapy was first evaluated as film-coated tablets in 2012 and received a positive opinion under EMA's Article 58 programme. (1)



This paediatric antimalarial formulation as well as the film-coated tablet formulation for adults and children weighing >20kg were developed by the product development partnership Medicines for Malaria Venture (MMV) and Shin Poong Pharmaceutical Co. Ltd., Republic of Korea. (2)

► (1) [EMA/CHMP Summary of opinion, 19 November 2015.](#)

(2) MMV Press release, 20 November 2015.

### Extensions of indications

#### Anthrax vaccine adsorbed for post-exposure protection

**Product name:** BioThrax®

**Dosage form:** Suspension for intramuscular or subcutaneous injection

**Class:** Anthrax vaccine; *ATC code:* J07AC

**Approval:** FDA

**Newly approved use:** Together with antibiotic treatment, to prevent disease after confirmed or suspected exposure to anthrax spores.

► [FDA News release, 23 November 2015.](#)

#### Ipilimumab to prevent melanoma recurrence

**Product name:** Yervoy®

**Dosage form:** Injection for intravenous infusion

**Class:** Antineoplastic, monoclonal antibody that blocks CTLA-4; *ATC code:* L01XC11

**Approval:** FDA

**Newly approved use:** Adjuvant therapy for patients with stage III melanoma, to lower the risk that the melanoma will return following surgery.

**Safety information:** The product carries a Boxed Warning about potential fatal immune-mediated adverse reactions and unusual severe side effects.

► [FDA News release, 28 October 2015.](#)

#### Nivolumab for renal cell cancer

**Product name:** Opdivo®

**Dosage form:** Concentrate for solution for infusion

**Class:** Antineoplastic agent, monoclonal antibody, PD-1 receptor blocker; *ACT code:* L01XC17

**Approval:** FDA (breakthrough therapy designation, fast track designation, priority review)

**Newly approved use:** Treatment of patients with advanced (metastatic) renal cell carcinoma who have received prior anti-angiogenic therapy.

► [FDA News release, 23 November 2015.](#)

#### Pembrolizumab for advanced non-small cell lung cancer

**Product name:** Keytruda®

**Dosage form:** For injection: lyophilized powder in single-use vial for reconstitution

**Class:** Antineoplastic; PD-1 pathway blocker; *ATC code:* L01XC18

**Approval:** FDA (breakthrough therapy designation, accelerated approval). Approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test, the first test designed to detect PD-L1 expression in non-small cell lung tumours.

**Newly approved use:** Treatment patients with advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and whose tumours express the PD-L1 protein.

**Notes:** Pembrolizumab was previously approved for advanced melanoma by FDA and EMA.

► [FDA News release, 2 October 2015.](#)

### WHO endorsements

#### Global Ebola virus and antibody reference standards

The WHO Expert Committee on Biological Standardization has endorsed two types of Ebola reference reagents as the global

## WHO endorsements

standards for use in laboratory tests. The reference reagents were developed within a short time by the National Institute for Biological Standards and Control (NIBSC) and are made available to laboratories around the world through the NIBSC web site ([www.nibsc.org/products/brm\\_product\\_catalogue.aspx](http://www.nibsc.org/products/brm_product_catalogue.aspx)). The first standard is used for testing alongside patient samples to detect Ebola infection. The second measures Ebola antibody levels following infection, or following immunization with candidate vaccines.

The two standards will enable accurate measurement of Ebola virus and antibody, making it possible to compare results from different tests and different laboratories. By minimizing fragmentation and duplication of research efforts these global standards will help accelerate the development of new Ebola vaccines.

► [MHRA Press release, 5 November 2015.](#)

**Malaria vaccine to be delivered in pilot projects**

The World Health Organization's Strategic Advisory Group of Experts on Immunization

(SAGE) and the Malaria Policy Advisory Committee (MPAC) jointly recommended the implementation of 3–5 large pilot projects to understand how best to deliver a vaccine that protects against malaria in young children. The vaccine must be given in three doses one month apart, followed by a fourth dose 18 months later. The main question is how to ensure that each child receives all four doses.

The vaccine, known as RTS,S or Mosquirix®, was approved in July 2015 by EMA under its Article 58 procedure for medicines used outside the EU, subject to WHO recommendations on its use. It acts against *P. falciparum*, the most deadly malaria parasite globally and the most prevalent in Africa. It offers no protection against *P. vivax* malaria, which predominates in many countries outside Africa. The vaccine is a complementary tool that could be added to – but not replace – the core package of proven measures to prevent, diagnose and treat malaria.

► [WHO News release, 23 October 2015.](#) ●

# Publications and events

## Development

### Sustainable development goals aim at health for all

Geneva – WHO has welcomed the launch of the 2030 Agenda for Sustainable Development and is committed to work with partners around the world to achieve the new Sustainable Development Goals (SDGs).

Building on the Millennium Development Goals (MDGs), the SDG agenda demonstrates unprecedented scope and ambition. Poverty eradication, health, education, and food security and nutrition remain priorities, but the 17 SDGs also encompass a broad range of economic, social and environmental objectives, as well as the promise of more peaceful and inclusive societies.

SDG 3, “Ensure healthy lives and promote well-being for all at all ages”, profiles health as a desirable outcome in its own right. However, health is also presented as an input to other goals, and a reliable measure of how well sustainable development is progressing in general. The health goal includes new targets for key issues such as the global HIV, tuberculosis and malaria epidemics as well as child mortality and maternal mortality, on which major progress has been made under the MDGs. It also covers non-communicable diseases; health security; reproductive, maternal, newborn, child and adolescent health and infectious diseases, as well as universal health coverage – a goal which WHO particularly welcomes as it expresses the very spirit of the new development

agenda, with its emphasis on equity and social inclusion that leaves no one behind.

► [WHO Statement, 25 September 2015.](#)

## Access to medicines

### WHO publishes updated essential medicines lists

Geneva – WHO has published its updated WHO Model Lists of Essential Medicines and Essential Medicines for Children (1). A range of direct-acting antiviral medicines for hepatitis C (sofosbuvir, simeprevir, daclatasvir, ledipasvir and ombitasvir) have been added, despite the high cost of some of these medicines. This inclusive approach aims to enable the selection of optimal treatment regimens and to promote competition. Four medicines for treatment of multi-drug resistant tuberculosis have also been added, including the first new medicines to be developed for this disease in decades (bedaquiline and delamanid). The list further includes 16 new and 30 existing cancer medicines that were found to be associated with substantial or highly relevant benefits. The report specifies the evidence upon which the decisions were taken.

The model list will influence the development of national Essential Medicines Lists worldwide. The authors of a comment published in *The Lancet* (2) have welcomed the report, noting that the concept of selecting a limited list of essential medicines is applicable across countries and settings as a means to implement the moral imperative of

assuring universal access to life-saving medicines. They further emphasized the importance of comprehensive essential medicine policies covering a wide range of aspects, such as appropriate research and development, financing mechanisms, generic policies including various measures to overcome patent barriers, quality assurance, supply systems, and safe and cost-effective use. The 2016 report of the Lancet Commission on Essential Medicines Policies (3) will recommend ways of implementing such policies through concrete actions at the national and global levels.

► (1) WHO Technical Report Series. The Selection and Use of Essential Medicines. Report of the WHO Expert Committee. 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). October 2015. Published online in advance of publication in print.

(2) Gray AL, Wirtz VJ, 't Hoen E, Reich MR, Hogerzeil HV. Essential medicines are still essential. *The Lancet*. 2015; 386:1601–3. DOI: [http://dx.doi.org/10.1016/S0140-6736\(15\)00514-0](http://dx.doi.org/10.1016/S0140-6736(15)00514-0).

(3) The Lancet. A new Lancet Commission on essential medicines. *Lancet* 2014; 384: 1642. DOI: [http://dx.doi.org/10.1016/S0140-6736\(14\)62017-1](http://dx.doi.org/10.1016/S0140-6736(14)62017-1)

### Medicines Patent Pool expands mandate to hepatitis C and tuberculosis

Geneva – The Medicines Patent Pool (MPP), the world's only voluntary licensing mechanism in public health, has announced an expansion of its mandate to hepatitis C and tuberculosis medicines.

Hepatitis C affects between 130 and 150 million people worldwide. Tuberculosis killed 1.5 million people globally in 2014 alone and has become a public health challenge particularly with

the emergence of multidrug-resistant strains of *Mycobacterium tuberculosis*. New treatments have been developed for both diseases, but they are unaffordable for many health systems.

Since its creation in 2010, the MPP has signed agreements for 12 antiretrovirals with six patent holders for countries that are home to 87-93% of people living with HIV in the developing world, saving the international community an estimated \$119.6 million from the procurement of low-cost HIV medicines. Building on its existing model, the MPP will seek to license for generic manufacture of new direct acting antivirals for hepatitis C as well as new and re-purposed medicines for tuberculosis.

► MPP Press release, 6 November 2015.

### First patent pool licence for a hepatitis C medicine

Geneva – The Medicines Patent Pool (MPP) has signed a licence with Bristol-Myers Squibb for the hepatitis C medicine daclatasvir. The royalty-free agreement allows manufacturers to develop daclatasvir for sale in 112 low- and middle-income countries, 76 of which are classified as middle-income nations by the World Bank. Nearly two thirds of all patients living with hepatitis C in the LMICs reside in the territory covered by this agreement.

Importantly, the licence allows generic manufacturers to develop fixed-dose combinations with other direct-acting antivirals to create powerful pan-genotypic regimens that offer the potential to treat all of the six major genotypes of HCV. Pan-genotypic regimens are crucial in resource-limited countries where access to genotype testing is limited. Bristol-Myers Squibb will provide a technology

transfer package and information needed for the manufacture and registration of the product. As all licences signed by the MPP, the full agreement is available on the MPP's website.

MPP Press release, 23 November 2015.

### Controlled substances not accessible to all in need

Kuala Lumpur – The Global Commission on Drug Policy (GCDP) has released a new report showing that 75% of the world's population does not have access to pain-relieving medicines included in the WHO Model List of Essential Medicines, because of strict drug control policies. Ninety-two percent of the world's supply of morphine is consumed by just 17% of the global population, with consumption primarily concentrated in North America and Europe.

The report notes that governments have an obligation under international law to ensure equitable access to controlled medicines for their populations, and that this obligation has equal importance as drug control measures to reduce illegal diversion. The upcoming UN General Assembly Special Session (UNGASS) on Drugs in New York in April 2016 will be an opportunity to address this major gap in access to controlled medicines. <sup>(1)</sup>

Aside from morphine and other opioid analgesics, ketamine – an anaesthetic – is one of the needed substances. In March 2015 a UN Commission vote on whether ketamine should be placed under international control had been postponed. The WHO Expert Committee on Drug Dependence (ECDD) has recommended against this measure on three separate occasions, in 2006, 2012 and 2014. In response to a request for more information from the UN Commission on Narcotic Drugs, the WHO Expert Committee

considered updated evidence on the issue at its 37<sup>th</sup> meeting on 16-20 November 2015. The material presented to the Committee confirmed the importance of the medical use of ketamine, particularly for low and middle income countries, and highlighted the potential role of ketamine as a prototype for a completely new class of antidepressants. The report did not find any changes with regard to global ketamine use and related medical problems, or abuse liability or toxicity. <sup>(2)</sup>

► <sup>(1)</sup> 24<sup>th</sup> International harm reduction conference, 18-21 October 2015, Kuala Lumpur, Malaysia. [Press release, 19 October 2015](#).  
Global Commission on Drug Policy. [The Negative Impact of Drug Control on Public Health: The Global Crisis of Avoidable Pain](#). October 2015.

<sup>(2)</sup> Ketamine (INN). Update Review Report. Agenda item 6.1. Expert Committee on Drug Dependence, Thirty-seventh Meeting. Geneva, 16-20 November 2015.

### Inefficiencies in the global insulin market

Health Action International (HAI) has released its first fact sheet from the ACCISS (Addressing the Challenges and Constraints of Insulin Sources and Supply) Study, which shows that one in two people in need of insulin cannot reliably access this life-saving medication because it is unavailable, unaffordable or both. The fact sheet provides an overview of the increasing global need for insulin to treat type 1 and type 2 diabetes and describes some of the barriers at national and global level that prevent millions of people from accessing insulin.

The three-year study, which was launched in early 2015, aims to identify the causes of poor insulin availability and unaffordable prices as a basis for

developing policies and interventions to improve access, particularly in the world's most under-served regions.

- ACCISS/HAI. [Inequities and Inefficiencies in the Global Insulin Market](#). Fact Sheet 1. 1<sup>st</sup> November 2015.

## Health and trade

### European Council resolution defends public health interests

Strasbourg – The Parliamentary Assembly of the Council of Europe has adopted a resolution titled “Public health and the interests of the pharmaceutical industry: how to guarantee the primacy of public health interests?”

The resolution recognizes the indisputable role that the pharmaceutical industry has played in medical advances. However, it notes that in recent years very few new medicines have been placed on the market which present “a real therapeutic benefit satisfying real health needs.” Prices for some medicines, such as cancer and hepatitis C treatments, have increased sharply placing a burden on public health systems. The resolution calls on member states to apply rules to limit rising prices and conflicts of interest. It also proposes to set up a public fund for independent research geared to address unmet health needs, and calls on the WHO to put forward alternatives to the current patent-based model for development of new medicines.

- Intellectual Property Watch. [Council Of Europe Issues Resolution, Questions Current IP System For Pharmaceutical Products](#). 1st October 2015.  
Parliamentary Assembly of the Council of Europe. [Resolution 2071 \(2015\) Provisional version](#).

### HAI/MSF report on EU trade policies and public health

Brussels – Médecins sans Frontières (MSF) and Health Action International (HAI) have launched their new report reviewing the European trade and investment policies, and have urged the European Union (EU) to close the gap between its public position to support access to affordable medicines and the current reality of its trade policies. The report recommends that countries should be supported in making use of the public health related flexibilities of the TRIPS Agreement to promote access to medicines.

The report comes as the European Trade Commissioner has presented her future trade and investment strategy. The European Commission has recently decided to support the world's poorest countries in their request for an indefinite exemption from implementing intellectual property rules on medicines until they are no longer classified as a least-developed country.

- HAI / MSF Press release, 14 October 2015.  
HAI / MSF Access Campaign. [Empty gestures: The EU's commitments to safeguard access to medicines](#). Review of the European Union's Trade & Investment Policy, 2015.

### WTO extends drug patent exemption for least-developed countries

Geneva – The World Trade Organization (WTO)'s Council for Trade-Related Aspects of Intellectual Property Rights (TRIPS) has agreed to extend until 2033 the period during which key provisions of the WTO's intellectual property agreement, the TRIPS Agreement, do not apply to pharmaceutical products in least-developed countries. The

decision also keeps open the option for further extensions beyond that date. The extension comes a month after the adoption of the new UN Sustainable Development Goals (SDGs), which affirm the right of developing countries to utilize TRIPS Agreement flexibilities to ensure access to medicines for all.

► [WTO News item, 6 November 2015.](#)

### New WHO publication about trade and health

Geneva – A new WHO publication explores the linkages between trade and health in today's globalized world, and the strategies that policy-makers can adopt in order to harness trade-related benefits and mitigate negative impacts in order to promote public health. It provides background information, makes recommendations for coherent policy-making on trade and health, reviews recent initiatives in trade and health capacity building and offers technical advice, from a public health perspective, on the implementation of trade treaties in national legislation. The book concludes with three chapters on sector-specific intersections between health and trade, including a chapter on trade in medicines, which examines the impact of trade-related mechanisms – especially aspects related to intellectual property protection – on medicines availability, and policy instruments used in different countries to strike a balance between public health and commercial interests.

► [Trade and Health: Towards building a National Strategy. Geneva: WHO, 2015.](#)

## Diseases

### Hepatitis world summit adopts Declaration

Glasgow - Over 400 global stakeholders representing over 90 countries gathered at the first-ever World Hepatitis Summit held in Glasgow on 2-4 October 2015 (1). Concluding the summit, the participants released the Glasgow Declaration on Hepatitis (2), which calls upon governments to develop and implement comprehensive, funded national plans and programmes for prevention, testing, diagnosis, care and treatment of hepatitis.

Around 400 million people are currently living with viral hepatitis. Claiming an estimated 1.45 million lives each year, the disease is one of the world's leading causes of death. The draft WHO Global Health Sector Strategy on Viral Hepatitis (3) proposes targets for reduction of incidence and mortality, and aims for treatment of 80% of eligible people with chronic hepatitis B and C infections. Medicinal treatments exist, but funding is the big question in view of their current high cost.

► (1) WHO. Hepatitis. [First World Hepatitis Summit \[web page\]](#).

(2) [Glasgow Declaration on Hepatitis.](#)

(3) [WHO Global Health Sector Strategy on Viral Hepatitis, 2016-2021. Draft for consultation.](#)

### Malaria death rates plunge but risk remains

London – WHO and UNICEF have launched their joint report on achieving the malaria millennium development goals (MDGs) (1).

The report (2) summarizes the remarkable progress seen in reversing malaria mortality and incidence. Between



2000 and 2015, malaria incidence fell by 37% globally and death rates by 60%. New research from the Malaria Atlas Project – a WHO Collaborating Centre based at the University of Oxford – shows that insecticide-treated nets have been by far the most important intervention across Africa (3).

However, serious bottlenecks remain in providing full access to malaria prevention, diagnostic testing and treatment. Progress has been uneven: fifteen countries – mainly in sub-Saharan Africa – bear the burden of 80% of malaria cases globally. Children under five account for more than two thirds of all malaria-associated deaths.

The World Health Assembly's 15-year road map for malaria control aims at a further 90% reduction in global malaria incidence and mortality by 2030. The WHO-UNICEF report notes that these targets can only be achieved with political will, country leadership and significantly increased investment. Annual funding will need to triple, from US\$ 2.7 billion today to US\$ 8.7 billion in 2030.

► (1) [WHO/UNICEF joint press release, 17 September 2015.](#)

(2) [Achieving the malaria MDG target: reversing the incidence of malaria 2000–2015.](#) WHO, UNICEF: September 2015.

(3) Bhatt S et al. [The effect of malaria control on \*Plasmodium falciparum\* in Africa between 2000 and 2015.](#) *Nature* (2015) doi:10.1038/nature15535. Published online, 16 September 2015.

### Tuberculosis remains a public health challenge

Geneva – The WHO has released its *Global tuberculosis report 2015*. The report shows a continuing decline in mortality, which has nearly halved since 1990. The number of new cases reported globally has fallen by 1.5% each year for

a total decrease of 18% since the year 2000. The millennium development goal to halt and reverse tuberculosis incidence by 2015 has been achieved globally and in 16 of the 22 high-burden countries that collectively account for 80% of cases.

However, tuberculosis remains a public health challenge. Tuberculosis and HIV now rank alongside each other as the infectious diseases with the highest numbers of deaths in the world. Each accounted for 1.1–1.2 million deaths in 2014.

To reduce the global burden of tuberculosis, detection and treatment gaps need to be closed, funding shortfalls filled and new diagnostics, medicines and vaccines developed. Detection and treatment gaps are especially serious among people with multidrug-resistant tuberculosis. Only about a quarter of an estimated 480 000 cases worldwide were detected and reported to national authorities in 2014. The major reason for these gaps is a shortfall in funding.

► [WHO News release, 20 October 2015.](#)

[WHO. Global tuberculosis report 2015. 20th Edition. Geneva: 2015.](#)

### Ebola still a public health emergency

Geneva – At its 7<sup>th</sup> meeting, the Emergency Committee convened by the WHO Director-General under the International Health Regulations has advised that the Ebola virus disease (EVD) outbreak continues to constitute a public health emergency of international concern. Two active chains of transmission continued in October 2015, one in Guinea and one in Sierra Leone. The Committee has updated its recommendation on measures to minimize the risk of international spread of EVD.

There should be no international travel of Ebola contacts or cases unless they are part of appropriate medical evacuation, and exit screening should be performed at the borders of States with Ebola transmission. On the other hand, there should be no general ban on international travel or trade, nor any restrictions on the travel of EVD survivors. (1)

On 7 November 2015 WHO declared that Ebola virus transmission in Sierra Leone had ended. Forty-two days after the last person confirmed to have Ebola virus disease had a second negative blood test, the country entered a 90-day period of enhanced surveillance. (2)

► (1) [WHO Statement, 5 October 2015](#).

(2) [WHO News release, 7 November 2015](#).

### **Measles immunization gap persists**

Geneva – WHO has reported that although an estimated 17.1 million lives have been saved since 2000 through measles vaccination, 2015 global milestones and measles elimination goals are off track. New published data shows that since 2010 overall progress towards increasing global immunization coverage has stagnated at 85% of children having received their first dose of measles vaccination, and only half of the world's children receiving the recommended second dose.

Despite successful implementation of vaccination campaigns in a number of countries, more than 100 000 children needlessly died from measles in 2014. Large outbreaks were reported from China, the Philippines, Viet Nam, Angola, Ethiopia, India, the Russian Federation and Somalia. Such outbreaks happen when there are gaps in vaccination programmes and continue to pose a

serious challenge to meeting global targets.

► [WHO News release, 12 November 2015](#).

### **Antiretroviral treatment**

#### **WHO recommends treatment for all people living with HIV**

Geneva – WHO has published new guidelines recommending that anyone infected with HIV should begin antiretroviral therapy (ART) as soon after diagnosis as possible. The recommendations are supported by recent findings from clinical trials confirming that early use of ART keeps people living with HIV alive, healthier and reduces the risk of transmitting the virus to partners.

WHO now also recommends that people at “substantial” risk of HIV should be offered preventive antiretroviral treatment. This should be seen as an additional prevention choice based on a comprehensive package of services, including HIV testing, counselling and support, and access to condoms and safe injection equipment.

The new recommendations increase the number of people eligible for ART from 28 million to 37 million people globally. The recommendations were developed as part of a comprehensive update of WHO guidelines on ART. They were published ahead of the full guidelines because of their potential for public health impact.

► [WHO News release, 30 September 2015](#).

#### **Updated optimal list of ARVs for children**

Geneva – The Inter-Agency Task Team (IATT) on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children and other groups is

focused on meeting the needs of children with HIV infection. The IATT has published an update to the Optimal and Limited-Use Paediatric ARV Formularies, for use by governments and implementing agencies. The lists provide guidance on optimal products that are most readily available on the market and comply with WHO treatment guidance. The IATT works with WHO and UNICEF to periodically review and update these formularies.

- [IATT. Update to the Optimal List of Paediatric ARV Formulations. Policy brief.](#)

## Antibiotics

### International summit on antibiotic resistance

Uppsala – Following the adoption of the global action plan on antimicrobial resistance by the World Health Assembly in May 2015, some 200 stakeholders and experts from all parts of the world met at the 2015 Uppsala Health Summit in October to engage in dialogue how to put this action plan into practice.

The discussions held at the summit are documented in a post-conference report, which calls for information and education, leadership from governments and international organizations, and delinking of peoples' incomes from antibiotics sales. It was further stressed that rational use requires access to diagnostics and data on resistance, which is lacking particularly in developing countries, and that communication, coordination and more analyses on the consequences of antibiotics resistance are needed, including analyses on the cost of inaction.

Research efforts to develop new antibiotics need to be intensified. While academia and small and medium size enterprises were seen as the most

appropriate place for the discovery of new antimicrobial compounds, the expertise and experience of the pharmaceutical industry will be important to increase the chance of success.

- [Uppsala Health Summit. Conference report points the way in the fight against antibiotic resistance \[web page\].](#) 9 October 2015.

### Use of veterinary antibiotics in Europe

European Union – The EMA has released its fifth report on sales of antibiotics used in animals. According to this report, overall sales in the period 2011-2013 have decreased by approximately 8%, with 11 countries reporting decreases and six countries reporting increases.

Sales data on veterinary antibiotics are collected annually as part of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project, which is a cooperation between the national authorities throughout the European Union (EU) and is coordinated by EMA. A total of 26 countries from the European Economic Area (EEA) contributed data for the fifth ESVAC report, which comes with an [interactive database tool](#). (1)

In November 2015, the EMA released its new strategy on antimicrobials adopted by its Committee for Veterinary Medicinal Products for public consultation. The strategy recognizes that antimicrobial resistance affects both animal and human health and sets clear objectives to help combat the threat of resistance which may arise from the use of antimicrobials in animals. Comments are invited until 29 February 2016. (2)

- (1) [EMA News, 15 October 2015.](#)  
(2) [EMA News, 17 November 2015.](#)

## Multi-country survey reveals misconceptions on antibiotic resistance

Geneva – A multi-country survey shows that people are confused about antibiotic resistance. Three quarters (76%) of respondents think it happens when the body becomes resistant to antibiotics, 66% believe that they are not at risk if they personally take their antibiotics as prescribed, and 44% think that it is only a problem for people who take antibiotics regularly. In fact, anyone, of any age, in any country can get an infection with bacteria that are resistant to antibiotics.

What people can do to address antibiotic resistance is also not well understood. For example, 64% of respondents believe that antibiotics can be used to treat colds and flu, and 32% believe they do not need to complete the prescribed course of treatment if they feel better. More than half (57%) feel there is not much they can do to stop antibiotic resistance, while 64% believe medical experts will solve the problem before it becomes too serious.

Another key finding of the survey was that almost three quarters (73%) of respondents said farmers should give fewer antibiotics to food-producing animals.

The survey findings coincide with the launch of a new WHO campaign 'Antibiotics: Handle with care' – a global initiative to improve understanding of the problem. Antibiotic resistance is one of the biggest health challenges of the 21st century and will require global behaviour change by individuals and societies.

► [WHO News release, 16 November 2015.](#)

## Lists and manuals

### Indicators to assess pharmacovigilance systems

Geneva – WHO has published a practical manual for assessment of pharmacovigilance systems, with indicators that can be understood by health care workers without formal training in monitoring and evaluation.

The proposed indicators are based on the expected functions of pharmacovigilance centres as described in the WHO's [Minimum Requirements for a Functional Pharmacovigilance System](#). They reflect the existing structures, the processes used, and the outcomes or impact achieved in pharmacovigilance systems.

Pharmacovigilance is critical to monitor the safety and safe use of medicines in public health programmes. The manual proposes a set of nine pharmacovigilance indicators for public health programmes. Pharmacovigilance is also a regulatory function. A subset of indicators from this manual has been included in the WHO harmonized tool for assessing a national regulatory agency (NRA).

The manual is published as version 1 (v1.0) to underscore its evolving nature. Feedback from user groups will be used in developing the subsequent versions.

► [WHO pharmacovigilance indicators. A practical manual for the assessment of pharmacovigilance systems.](#) Geneva; WHO: 2015.

### Specifications for selected HIV diagnostics

Geneva – WHO, in collaboration with a wide range of institutions constituting the technical working group for procurement specifications of HIV diagnostics, has

published its updated technical report to support efficient procurement of essential equipment and laboratory commodities for HIV. This procurement tool covers all laboratory items approved for procurement by WHO and the Global Fund.

The manual includes lists of laboratory items required to perform HIV-related tests on specific defined technology, specifications of the items to facilitate their procurement, examples of quantities of reagents required to perform 1000 tests, and price benchmarks that will continue to be updated based on procurement of the contributing partners. This information assists professionals in understanding the different technologies and their cost implications, and in ensuring that all items are ordered in adequate quantities.

- [Specifications and quantities for efficient procurement of essential equipment and laboratory commodities for HIV](#). Second Edition. July 2015.

## WHO matters

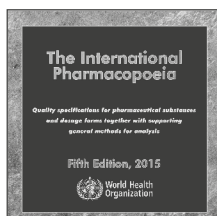
### WHO launches independent assessment of snake antivenoms

Geneva – In response to the current crisis in the supply of antivenoms, WHO has decided to offer an independent assessment of antivenoms. A call to manufacturers of antivenoms intended for use in sub-Saharan Africa was sent out in December 2015 (1).

About 5 million people are bitten by snakes every year, causing around 125 000 deaths and 400 000 people to be permanently disabled or disfigured. News that one of the most effective treatments for snake bite, Fav-Afrique, will run out in 2016 has caused dismay among public health experts and has spurred media interest in the subject. A prequalification scheme for antivenoms could incentivize manufacturers to develop and produce affordable, good quality antivenoms. Financial backing from donors will be needed to address this issue, on which WHO has attempted to raise the alarm for a number of years. WHO also encourages

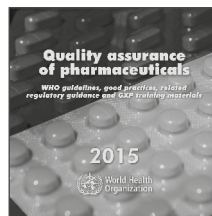
Just published!

#### CD ROM International Pharmacopoeia Fifth Edition, 2015.



#### CD ROM Quality Assurance of Pharmaceuticals. Update 2015.

WHO medicines quality assurance guidelines, good practices documents and training modules.



Order online: [www.who.int/bookorders](http://www.who.int/bookorders)

research to develop new therapeutic options for snakebites. (2)

WHO prequalification is open to a range of priority medical products by invitation for expression of interest (3). In November 2015 updated invitations were published for active pharmaceutical ingredients (API), for reproductive health medicines and for medicines to treat HIV infection and related diseases, including treatments for hepatitis B and C.

- (1) [WHO Prequalification update, 4 December 2015.](#)
- (2) [WHO Prequalification update, 2 October 2015.](#)
- (3) [WHO Prequalification. Invitations for Expressions of Interest \(EOIs\) \[web page\].](#)

### WHO Expert Committees on medicines meet in Geneva

Geneva – The WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) held its 50<sup>th</sup> meeting in Geneva on 12–16 October 2015. The experts adopted a number of monographs and texts for *The International Pharmacopoeia* as well as new and revised WHO guidelines.

Some important new guidance has been adopted. Good pharmacopoeial practices, as recommended by a group of world pharmacopoeias, will support convergence and could reduce the costs caused by differences among standards. In collaboration with the International Pharmaceutical Federation (FIP), guidance has been developed on points to consider in the preparation of children-specific medicines that are not available as authorized products. New guidance has also been adopted on regulatory control of variations and on conducting medicines quality surveys. The finalized

guidelines will be published as annexes to the WHO Technical Report Series in 2016. The working versions are available on the WHO web site.

The WHO Expert Committees on Biological Standardization and on the Selection and Use of Essential Medicines, as well as the International Nonproprietary Names (INN) Expert Group, met concurrently with the ECSPP and provided their updates and input on some cross-cutting issues.

- [WHO Essential medicines and health products. 50<sup>th</sup> Expert Committee on Specifications for Pharmaceutical Preparations \[web page\].](#)

### New web site on substandard and falsified medicines

Geneva – WHO has launched a new website on substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medical products, with answers to frequently asked questions and links to related information and WHO activities, such as the global WHO surveillance and monitoring system.

The existence of SSFFC products is an unacceptable risk to public health. They affect every region of the world, harm patients and undermine confidence in medical products, healthcare professionals and health systems. SSFFC products from every category have been reported. WHO is working with stakeholders to minimize the risks from SSFFC medical products by collecting data and transferring knowledge and good practices to countries.

- [WHO Essential Medicines and health products. Substandard, Spurious, Falsely labelled, Falsified and Counterfeit \(SSFFC\) Medical Products \[web site\].](#) ●

# Consultation documents

To receive draft monographs by email please contact Mrs Wendy Bonny (bonnyw@who.int), specifying that you wish to be added to the electronic mailing list.

## The International Pharmacopoeia

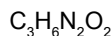
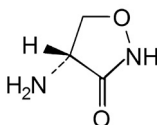
### Cycloserine (Cycloserinum)

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.638, August 2015).

The working document with line numbers and tracked changes is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/). Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: [schmidt@who.int](mailto:schmidt@who.int).

*[Note from the Secretariat. Following up on information received from a customer of The International Pharmacopoeia it is proposed to revise the monograph on Cycloserine.]*

*[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and ~~delete~~ in the working document available at the above-mentioned web address.]*



**Relative molecular mass.** 102.1.

**Chemical name.** (4R)-4-aminoisoxazolidin-3-one; (4R)-4-amino-1,2-oxazolidin-3-one; (+)-4-amino-3-isoxazolidinone; CAS Reg. No. 68-41-7.

**Description.** A white or pale yellow, crystalline, powder.

**Solubility.** Freely soluble in water; slightly soluble in methanol R and propylene glycol R; very slightly soluble in ethanol (~750 g/L) TS; practically insoluble in dichloromethane R.

**Category.** Antibacterial drug; antituberculosis drug.

**Storage.** Cycloserine should be kept in a tightly closed container.



**Additional information.** Cycloserine is slightly hygroscopic and degrades upon exposure to a humid atmosphere, decomposition being faster at higher temperatures.

## Requirements

**Definition.** Cycloserine is an analogue of the amino acid D-alanine with broad-spectrum antibiotic and glycinergic activities produced by *Streptomyces garyphalus* and *Streptomyces orchidaceus* or obtained by synthesis.

Cycloserine contains not less than 98.5% and not more than 101.5% of cycloserine ( $C_3H_6N_2O_2$ ), calculated with reference to the dried substance.

## Identity tests

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

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 4 volumes of 1-butanol R, 1 volume of glacial acetic acid R and 2 volumes of water R as the mobile phase. Apply separately to the plate 10  $\mu$ L of each of the following two solutions. For solution (A) dissolve 20 mg of the test substance in 0.5 mL of water R, add 4.5 mL of methanol R and shake. For solution (B) use 20 mg of cycloserine RS prepared in the same manner. After removing the plate from the chromatographic chamber allow it to dry exhaustively in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

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

A.2 Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using the conditions described above under test A.1, but using silica gel R5 as the coating substance. After removing the plate from the chromatographic chamber allow it to dry in a current of air and place the plate in a chamber with iodine vapours. Examine the chromatogram in daylight.

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

B. Dissolve about 1 mg in 10 mL of sodium hydroxide (0.1 mol/L) VS. To 1 mL of the resulting solution add 3 mL of acetic acid (~60 g/L) TS and 1 mL of a recently prepared mixture of equal volumes of a 40 mg/mL solution of sodium nitroprusside R and sodium hydroxide (~200 g/L) TS; a blue colour gradually develops.

C. The absorption spectrum (1.6) of a freshly prepared 25  $\mu$ g/mL solution in hydrochloric acid (0.1 mol/L) VS, when observed between 215 nm and 360 nm, exhibits a maximum at about 219 nm; the specific absorbance ( $A_{1cm}^{1\%}$ ) is between 327 and 361.

D. Carry out the examination as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum is concordant with the spectrum obtained from cycloserine RS or with the reference spectrum of cycloserine.

**Specific optical rotation (1.4).** Use a 50 mg/mL solution in sodium hydroxide (~80 g/l) TS and calculate with reference to the dried substance;  $[\alpha]_D^{20} = +108^\circ$  to  $+114^\circ$ .

**Heavy metals.** Use 2.0 g for the preparation of the test solution as described under [2.2.3 Limit test for heavy metals](#), Procedure 3; determine the heavy metals content according to Method A; not more than 10 µg/g.

**Sulfated ash (2.3).** Not more than 5.0 mg/g.

**Loss on drying.** Dry at 60°C under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) for 3 hours; it loses not more than 10 mg/g.

**pH value (1.13).** pH of a 100 mg/mL solution in carbon-dioxide-free water R, 5.5 to 6.5.

### Related substances

Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).

The mobile phases for gradient elution consist of a mixture of mobile phase A and mobile phase B using the following conditions:

Mobile phase A: 4 volumes of acetonitrile R, 70 volumes of 0.02 mol/L sodium octanesulfonate R solution, 10 volumes of phosphate buffer pH 2.8 and 16 volumes of water R.

Mobile phase B: 17 volumes of acetonitrile R, 70 volumes of 0.02 mol/L sodium octanesulfonate R solution, 10 volumes of phosphate buffer pH 2.8 and 3 volumes of water R.

Prepare the sodium octanesulfonate solution by dissolving 4.7 g of sodium octanesulfonate R in 1000 mL of water R.

Prepare the phosphate buffer pH 2.8 by dissolving 27.2 g of potassium dihydrogen phosphate R in 800 mL of water R, adjust the pH to 2.8 by adding phosphoric acid (~20 g/L) TS and dilute to 1000 mL with water R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–16	100	0	Isocratic
16–18	100 to 0	0 to 100	Linear gradient
18–22	0	100	Isocratic
22–24	0 to 100	100 to 0	Return to initial composition
24–30	100	0	Re-equilibration

Prepare the following solutions in mobile phase A. For solution (1) use a solution containing 1.0 mg of the test substance per mL. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 5.0 µg of cycloserine per mL. For solution (3) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 25 µg of cycloserine per mL. Heat carefully in a boiling water-bath for 30 minutes. For solution (4) use a solution containing 2.0 µg of D-serine R per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 195 nm.

Maintain the column temperature at 45°C.

Inject 50  $\mu\text{L}$  of solution (3). The test is not valid unless the resolution between the principal peak corresponding to cycloserine (retention time about 14 min) and the large degradation peak with a relative retention time of about 0.23 is not less than 20.

Inject alternately 50  $\mu\text{L}$  each of solutions (1), (2) and (4).

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to cycloserine (retention time about 14 minutes): impurity B (D-serine) about 0.23, impurity C about 0.35 and impurity A about 1.8.

In the chromatogram obtained with solution (1):

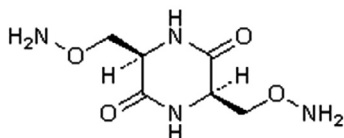
- the area of any peak corresponding to impurity B (D-serine) is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);
- the area of any other peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);
- the sum of the areas of all peaks, other than the principal peak and any peak corresponding to impurity B (D-serine), is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

### Assay

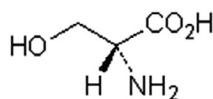
Dissolve about 0.1 g, accurately weighed, in 5 mL of water R. Add 75 mL of 2-propanol R and titrate with carbonate-free sodium hydroxide (0.1 mol/L) VS using thymolphthalein/ ethanol TS as indicator. Perform a blank determination and make any necessary correction.

Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 10.21 mg of  $\text{C}_3\text{H}_6\text{N}_2\text{O}_2$ .

### Impurities



A. (3*R*,6*R*)-3,6-bis[(aminooxy)methyl]piperazine-2,5-dione (cycloserine dimer),



B. (2*R*)-2-amino-3-hydroxypropanoic acid (D-serine),

C. condensation product with unknown structure.

\*\*\*

## Cycloserine capsules (Cycloserini capsulae)

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.637, August 2015).

The working document with line numbers and tracked changes is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/). Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: [schmidt@who.int](mailto:schmidt@who.int).

*[Note from the Secretariat. Following up on information received from a customer of The International Pharmacopoeia it is proposed to revise the monograph on Cycloserine capsules.]*

*[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and ~~delete~~ in the working document available at the above-mentioned web address.]*

**Category.** Antibacterial drug; antituberculosis drug.

**Storage.** Cycloserine capsules should be kept in a tightly closed container.

**Additional information.** Strength in the current WHO Model List of Essential Medicines (EML): 250 mg. Strength in the current EML for children: 250 mg.

### Requirements

Comply with the monograph for [Capsules](#).

**Definition.** Cycloserine capsules contain Cycloserine. They contain not less than 90.0% and not more than 110.0% of the amount of cycloserine ( $C_3H_6N_2O_2$ ) stated on the label.

**Manufacture.** The manufacturing process and the product packaging are designed and controlled so as to minimize the moisture content of the capsules. They ensure that, if tested, the contents of the capsules would comply with a loss on drying limit of not more than 20 mg/g when determined by drying a suitable quantity of the contents of the capsules for 3 hours under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) at 60°C.

### Identity tests

- Either tests A and B or tests B and C may be applied.

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 4 volumes of 1-butanol R, 1 volume of glacial acetic acid R and 2 volumes of water R as the mobile phase. Apply separately to the plate 10 µL of each of the following two solutions. For solution (A) shake a quantity of the contents of the capsules equivalent to 40 mg of cycloserine with 1 mL of water R, add 9 mL of methanol R, shake again, filter and use the filtrate. For solution (B) dissolve 20 mg of cycloserine RS in 0.5 mL of water R, add 4.5 mL of methanol R and shake. After removing the plate from the chromatographic chamber allow it to dry exhaustively in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

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

- A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described above under test A.1, but using silica gel R5 as the coating substance. After removing the plate from the chromatographic chamber allow it to dry in a current of air and place the plate in a chamber with iodine vapours. Examine the chromatogram in daylight.

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

- B. Shake a quantity of the contents of the capsules containing 10 mg of cycloserine with 100 mL of sodium hydroxide (~40 g/L) TS and filter. To 1 mL of the filtrate add 3 mL of acetic acid (~60 g/L) TS and 1 mL of a recently prepared mixture of equal volumes of a 40 mg/mL solution of sodium nitroprusside R and sodium hydroxide (~200 g/L) TS; a blue colour gradually develops.
- C. See the test described under "Assay", Method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

### Related substances

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

Prepare the following solutions in mobile phase A. For solution (1) transfer a quantity of the contents of the capsules containing 100 mg of cycloserine into a 100 mL volumetric flask. Add about 70 mL, shake for 5 minutes, make up to volume and filter. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration containing 5.0 µg of cycloserine per mL. For solution (3) dilute a suitable volume of solution (1) to obtain a concentration of 25 µg of cycloserine per mL. Heat carefully in a boiling water-bath for 30 minutes. For solution (4) use a solution containing 2.0 µg of D-serine R per mL.

Inject 50 µL of solution (3). The test is not valid unless the resolution between the principal peak corresponding to cycloserine (retention time about 14 minutes) and the large degradation peak with a relative retention time of about 0.23 is not less than 20.

Inject alternately 50 µL each of solutions (1), (2) and (4).

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to cycloserine (retention time about 14 minutes): impurity B (D-serine) about 0.23, impurity C about 0.35 and impurity A about 1.8.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B (D-serine) is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.4%);
- the area of any other peak, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);
- the sum of the areas of all peaks, other than the principal peak and any peak corresponding to impurity B (D-serine), is not greater than six times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Assay**

- Either method A or method B may be applied.
- A. Carry out the assay as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).

The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 4 volumes of acetonitrile R, 70 volumes of a 0.02 mol/L sodium octanesulfonate R solution, 10 volumes of phosphate buffer pH 2.8 and 16 volumes of water R.

Mobile phase B: 17 volumes of acetonitrile R, 70 volumes of a 0.02 mol/L sodium octanesulfonate R solution, 10 volumes of phosphate buffer pH 2.8 and 3 volumes of water R.

Prepare the sodium octanesulfonate solution by dissolving 4.7 g of sodium octanesulfonate R in 1000 mL of water R.

Prepare the phosphate buffer pH 2.8 by dissolving 27.2 g of potassium dihydrogen phosphate R in 800 mL of water R, adjust the pH to 2.8 by adding phosphoric acid (~20 g/L) TS and dilute to 1000 mL with water R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–16	100	0	Isocratic
16–18	100 to 0	0 to 100	Linear gradient
18–22	0	100	Isocratic
22–24	0 to 100	100 to 0	Return to initial composition
24–30	100	0	Re-equilibration

Prepare the following three solutions in mobile phase A. For solution (1) weigh and mix the contents of 20 capsules and transfer a quantity of the contents containing about 10 mg of cycloserine, accurately weighed, into a 100 mL volumetric flask. Add about 70 mL, shake for 5 minutes, make up to volume and filter. For solution (2) use 0.1 mg of cycloserine RS per mL. For solution (3) dilute a suitable volume of solution (1) to obtain a concentration of 25 µg of cycloserine per mL. Heat carefully in a boiling water-bath for 30 minutes.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 195 nm.

Maintain the column temperature at 45°C.

Inject 50 µL of solution (3). The test is not valid unless the resolution between the principal peak corresponding to cycloserine (retention time about 14 minutes) and the large degradation peak with a relative retention time of about 0.23 is not less than 20.

Inject alternately 50 µL each of solutions (1) and (2).

Measure the areas of the peaks responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of cycloserine ( $C_3H_6N_2O_2$ ) in the capsules, using the declared content of  $C_3H_6N_2O_2$  in cycloserine RS.

- B. Weigh and mix the contents of 20 capsules and transfer a quantity of the contents containing 0.250 g of cycloserine, accurately weighed, into a 200 mL volumetric flask. Add hydrochloric acid (0.1mol/L) VS to volume, shake for 10 minutes and filter. Dilute 2 mL of the filtrate to 100 mL with hydrochloric acid (0.1mol/L) VS.

Measure the absorbance (1.6) of this solution in a 1 cm layer at the maximum at about 219 nm against a solvent cell containing hydrochloric acid (0.1mol/L) VS.

Calculate the content of cycloserine ( $C_3H_6N_2O_2$ ) in the capsules, using an absorptivity value of 34.3 ( $A_{1cm}^{1\%} = 343$ ).

### Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph for Cycloserine.

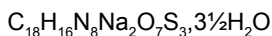
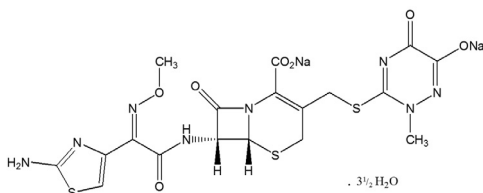
\*\*\*



## Ceftriaxone sodium (*Ceftriaxonum natricum*)

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.644, November 2015).

The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/). Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: [schmidth@who.int](mailto:schmidth@who.int).



**Relative molecular mass.** 661.60

**Chemical name.** Disodium (6R,7R)-7-[[[(2Z)-(2-aminothiazol-4-yl)(methoxyimino) acetyl] amino]-3-[[[(2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulfanyl]meth- yl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 3.5 hydrate.

**Description.** Almost white or yellowish, slightly hygroscopic, crystalline powder.

**Solubility.** Freely soluble in water, sparingly soluble in methanol, very slightly soluble in anhydrous ethanol.

**Labelling.** The label states, where applicable:

- that the substance is free of bacterial endotoxins;
- that the substance is sterile.

**Category.** Antibacterial

**Storage.** Ceftriaxone sodium should be kept in an air-tight container protected from light. If the substance is sterile, store in a sterile and air-tight container protected from light.

### Requirements

Ceftriaxone sodium contains not less than 96.0% and not more than 102.0% of the labelled amount of ceftriaxone sodium ( $\text{C}_{18}\text{H}_{16}\text{N}_8\text{Na}_2\text{O}_7\text{S}_3$ ), calculated with reference to the anhydrous substance.

### Identity tests

- Either tests A and C or tests B and C may be applied.
- A. Carry out the examination as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum is concordant with the spectrum obtained from ceftriaxone sodium RS or with the reference spectrum of ceftriaxone sodium.

- B. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given under the Assay test. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak corresponding to ceftriaxone in the chromatogram obtained with solution (2).
- C. When tested for sodium as described under [2.1 General identification tests](#), yields the characteristic reaction.

**Specific optical rotation** (1.4). Dissolve 0.250 g in water R and dilute to 25.0 mL with the same solvent. Calculate with reference to the anhydrous substance;  $[\alpha]_D^{20^\circ} = -155^\circ$  to  $-170^\circ$ .

**Clarity and colour of solution.** Dissolve 2.40 g in carbon-dioxide-free water R and dilute to 20.0 mL with the same solvent (Solution A). Dilute 2 mL of Solution A to 20 mL carbon-dioxide-free water R. The solution is clear and not more intensely coloured than reference solution YW2 when compared as described under [1.11 Colour of liquids](#). (Keep the remaining solution (Solution A) for the “pH value”.)

**pH value** (1.13). pH of the solution prepared for the “Clarity and colour of solution” (Solution A), 6.0 to 8.0.

**Water.** Determine as described under [2.8 Determination of water by the Karl Fischer method](#), method A, using about 0.1 g of the test substance. The water content is not less than 80 mg per g and not more than 110 mg per g.

**Bacterial endotoxins.** If intended for use in the manufacture of a parenteral dosage form without a further appropriate procedure for the removal of bacterial endotoxins, carry out the test as described under [3.4 Test for bacterial endotoxins](#); contains not more than 0.20 IU of endotoxin per mg of ceftriaxone sodium.

#### Related substances

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given below under assay method.

Prepare the following solutions in mobile phase: for solution (1) dissolve about 30 mg of the test substance and dilute to 100.0 mL. For solution (2) dilute 1 volume of solution (1) to 100 volumes. For solution (3) dissolve about 5 mg ceftriaxone sodium RS and 5 mg of ceftriaxone impurity G to 100.0 mL.

Inject 20  $\mu$ L of solution (3). The test is not valid unless the resolution factor between the peaks due to ceftriaxone and ceftriaxone impurity G is at least 3.0. Ceftriaxone impurity G is eluted at a relative retention of 1.4 with reference to ceftriaxone (retention time about 9 min).

Inject alternately 20  $\mu$ L each of solution (1) and (2). Record the chromatograms for about 2 times the retention time of ceftriaxone. The chromatogram obtained with solution (1) may show the following impurities at the following relative retention with reference to ceftriaxone: impurity A: about 0.2; impurity B: about 0.34; impurity C: about 0.62; impurity D: about 0.72; impurity E: about 0.78; impurity F: about 1.3 and impurity G: about 1.4.

In the chromatogram obtained with solution (1):

- the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0 %);
- the sum of the areas of all peaks, other than the principal peak, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5 %). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

## Assay

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (25 cm x 4.6 mm) packed with particles of base-deactivated silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm) <sup>1</sup>.

As the mobile phase use a solution prepared as follows: dissolve 2.0 g of tetradecylammonium bromide R and 2.0 g of tetraheptylammonium bromide R in a mixture of 440 mL of water R, 55 mL of phosphate buffer pH 7.0 (0.067 mol/L) TS, 5.0 mL of citrate buffer pH 5.0 TS and 500 mL of acetonitrile R and filter.

Prepare the following solutions in mobile phase. For solution (1) dissolve 30 mg of the test substance, accurately weighed and dilute to 100.0 mL. For solution (2) dissolve about 30 mg of ceftriaxone sodium RS, accurately weighed and dilute to 100.0 mL. For solution (3) dissolve about 5 mg ceftriaxone sodium RS and about 5 mg of ceftriaxone impurity G and dilute to 100.0 mL.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the peaks due to ceftriaxone and ceftriaxone impurity G is at least 3.0.

Inject alternately 20 µL each of solution (1) and (2). Measure the areas of the peaks corresponding to ceftriaxone and calculate the percentage content of ceftriaxone sodium ( $C_{18}H_{16}N_8Na_2O_7S_3$ ) with reference to the anhydrous substance.

**Sterility.** If intended for use in the manufacture of a parenteral dosage form without a further appropriate sterilization procedure, complies with [3.2 Test for sterility](#).

## Impurities

*[Note from the Secretariat. The structures of the impurities will be added at a later stage.]*

- A. (Z)-2-(2-Aminothiazol-4-yl)-N-[(5aR,6R)-1,7-dioxo-1,3,4,5a,6,7-hexahydroazeto[2,1-b]furo[3,4-d][1,3]thiazin-6-yl]-2-(methoxyimino)acetamide. (Deacetylcefotaxime lactone)
- B. (6R,7R)-3-(Acetoxymethyl)-7-amino-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. (7-Aminocephalosporanic acid)
- C. 3-Mercapto-2-methyl-1,2-dihydro-1,2,4-triazine-5,6-dione. (Ceftriaxone triazine analog)
- D. (Z)-S-Benzothiazol-2-yl 2-(2-aminothiazol-4-yl)-2-(methoxyimino)thioacetate (Ceftriaxone benzothiazolyl oxime).
- E. (6R,7R)-7-Amino-3-[[[(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (Deacyl ceftriaxone).
- F. (6R,7R)-7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[[[(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid (Ceftriaxone 3-ene isomer).
- G. (6R,7R)-7-[(E)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[[[(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (Ceftriaxone E-isomer).

## Reagent to be included:

Citrate buffer, pH 5 TS

**Procedure.** Dissolve 20.17 g of citric acid R in 800 mL of water R, adjust to pH 5.0 with sodium hydroxide (~400 g/L) TS and dilute to 1000 mL with water R.

\*\*\*

<sup>1</sup> Hypersil BDS C18 has been found suitable.

## Ceftriaxone for injection (*Ceftriaxoni ad injectionem*)

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.645, November 2015).

The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/). Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: [schmidt@who.int](mailto:schmidt@who.int).

**Description.** A white and almost white powder.

**Category.** Antibacterial.

**Storage.** Ceftriaxone for injection should be stored in a tightly closed container. The reconstituted solution should be used immediately after preparation.

**Additional information.** Strengths in the current WHO Model List of Essential Medicines (EML): 250 mg, 1 g (as sodium salt) in vial. Strength in the current WHO EML for children: 250 mg, 1 g (as sodium salt) in vial.

### Requirements

The powder for injection and the reconstituted solution for injections comply with the monograph on [Parenteral preparations](#).

**Definition.** Ceftriaxone for injection is a sterile powder containing Ceftriaxone sodium with or without excipients.

Ceftriaxone for injection contains not less than 90.0% and not more than 110.0% of the labelled amount of ceftriaxone ( $C_{18}H_{18}N_8O_7S_3$ ).

### Identity tests

- Either tests A and C or tests B and C may be applied.
- A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from ceftriaxone sodium RS or with the reference spectrum of ceftriaxone sodium.
- B. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given under "Assay". The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the ceftriaxone peak in the chromatogram obtained with solution (2).
- C. When tested for sodium as described under [2.1 General identification tests](#), yields the characteristic reaction.

**Water.** Determine as described under [2.8 Determination of water by the Karl Fischer method](#), method A, using about 0.1 g of the powder. The water content is not more than 110 mg per g.

**Clarity and colour of solution.** Dissolve 2.40 g in carbon-dioxide-free water R and dilute to 20.0 mL with the same solvent (Solution A). Dilute 2 mL of Solution A to 20 mL carbon-dioxide-free water R. The solution is clear and not more intensely coloured than reference solution YW2 when compared as described under [1.11 Colour of liquids](#). (Keep the remaining solution (Solution A) for the “pH value”.)

**pH value** ([1.13](#)). pH of the solution prepared for the “Clarity and colour of solution” (Solution A), 6.0 to 8.0.

**Bacterial endotoxins.** Carry out the test described under [3.4 Test for bacterial endotoxins](#), contains not more than 0.19 IU of endotoxin per mg of ceftriaxone.

### Related substances

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given below under assay method.

Prepare the following solutions in mobile phase: for solution (1) dissolve about 30 mg of the powder and dilute to 100.0 mL. For solution (2) dilute 1 volume of solution (1) to 100 volumes. For solution (3) dissolve about 5 mg ceftriaxone sodium RS and 5 mg of ceftriaxone impurity G to 100.0 mL.

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the peaks due to ceftriaxone and ceftriaxone impurity G is at least 3.0. Ceftriaxone impurity G is eluted at a relative retention of 1.4 with reference to ceftriaxone (retention time about 9 min).

Inject alternately 20 µL each of solutions (1) and (2). Record the chromatograms for about 2 times the retention time of ceftriaxone. The chromatogram obtained with solution (1) may show the following impurities at the following relative retention with reference to ceftriaxone: impurity A: about 0.2; impurity C: about 0.62; impurity D: about 0.72; impurity E: about 0.78; impurity F: about 1.3 and impurity G: 1.4.

In the chromatogram obtained with solution (1)

- the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0 %);
- the sum of the areas of all peaks, other than the principal peak, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

### Assay

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (25 cm x 4.6 mm) packed with particles of base-deactivated silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm) <sup>2</sup>.

As the mobile phase use a solution prepared as follows: dissolve 2.0 g of tetradecylammonium bromide R and 2.0 g of tetraheptylammonium bromide R in a mixture of 440 mL of water R, 55 mL of phosphate buffer, pH 7.0 (0.067 mol/L) TS, 5.0 mL of a citrate buffer pH 5.0 TS and 500 mL of acetonitrile R and filter.

<sup>2</sup> Hypersil BDS C18 has been found suitable.

Prepare the following solutions in mobile phase: for solution (1) determine the weight of the contents of 10 containers. Transfer a quantity of the mixed contents containing about 30 mg of ceftriaxone, accurately weighed, to a 100 mL volumetric flask, dissolve and dilute to volume. For solution (2) dissolve about 35 mg of ceftriaxone sodium RS, accurately weighed and dilute to 100.0 mL. For solution (3) dissolve about 5 mg ceftriaxone sodium RS and 5 mg of ceftriaxone impurity G to 100.0 mL.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the peaks due to ceftriaxone and ceftriaxone impurity G is at least 3.0.

Inject 20 µL of solution (1) and (2) Measure the areas of the peaks corresponding to ceftriaxone and calculate the content of ceftriaxone ( $C_{18}H_{18}N_8O_7S_3$ ) per container. Each mg of  $C_{18}H_{16}N_8Na_2O_7S_3$  is equivalent to 0.9274 mg of  $C_{18}H_{18}N_8O_7S_3$ .

### Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph for Ceftriaxone sodium.

\*\*\*

# ATC/DDD classification

The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) as a measuring unit are tools for exchanging and comparing data on drug use at international, national or local levels. The ATC/DDD system has become the gold standard for international drug utilization research. It is maintained by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway.

Visit [www.whocc.no/](http://www.whocc.no/) for more information.

## ATC/DDD classification (temporary)

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in October 2015.

Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology before 1 February 2016. If no objections are received before this date, the new ATC codes and DDDs will be considered final and included in the **January 2017 version of the ATC/DDD Index**.

### New ATC 5<sup>th</sup> level codes:

*Please note that the list does not include new ATC codes established as a result of ATC alterations.*

ATC level name/INN	ATC code
aceneuramic acid	M09AX05
alectinib	L01XE36
alirocumab	C10AX14
aminobenzoate potassium	D11AX23
arterolane and piperazine	P01BX02
carvedilol and ivabradine	C07FX06
cobimetinib	L01XE38
daratumumab	L01XC24
deoxycholic acid	D11AX24
desfesoterodine	G04BD13
edoxaban	B01AF03
elbasvir and grazoprevir	J05AX68
elotuzumab	L01XC23
eluxadoline	A07DA06
empegfilgrastim	L03AA16
etelcalcetide	H05BX04
ferric maltol	B03AB10
fluoroethyl-L-tyrosine ( <sup>18</sup> F)	V09IX10
follitropin delta	G03GA10

/Continued



*New ATC 5<sup>th</sup> level codes, continued*

ATC level name/INN	ATC code
gallium ( <sup>68</sup> Ga) endoreotide	V09IX09
inotuzumab ozogamicin	L01XC26
ixekizumab	L04AC13
landiolol	C07AB14
metoprolol and ivabradine	C07FX05
metreleptin	A16AA07
mogamulizumab	L01XC25
osimertinib	L01XE35
phenylephrine and ketorolac	S01FB51
rociletinib	L01XE37
safinamide	N04BD03
salbutamol and beclometasone	R03AK13
talimogene laherparepvec	L01XX51
tiazotic acid	C01EB23
tramadol and dextetopfen	N02AJ14
trientine	A16AX12

*New ATC level codes (other than 5<sup>th</sup> levels):*

ATC level name	ATC code
Beta blocking agents, other combinations	C07FX
Glucagon-like peptide-1 receptor (GLP-1) analogues	A10BJ
Opioids in combination with non-opioid analgesics	N02AJ
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	A10BK

*Change of ATC codes:*

ATC level name/INN	Previous ATC code	New ATC code
albiglutide	A10BX13	A10BJ04
canagliflozin	A10BX11	A10BK02
dapagliflozin	A10BX09	A10BK01
dulaglutide	A10BX14	A10BJ05
empagliflozin	A10BX12	A10BK03
exenatide	A10BX04	A10BJ01
liraglutide	A10BX07	A10BJ02
lixisenatide	A10BX10	A10BJ03
mepolizumab	L04AC06	R03DX09
methotrexate <sup>1)</sup>	L01BA01	L04AX03 <sup>1)</sup>
nonacog alfa	B02BD09	B02BD04 <sup>2)</sup>
tiopronin	R05CB12	G04BX16
trenonacog alfa	B02BD12	B02BD04 <sup>2)</sup>

1) Splitting of ATC code. Only the classification of pre-filled syringes of methotrexate for use in non-cancer indications is changed. These products will be moved to the existing ATC code for oral administered product of methotrexate. Parenteral preparations used for treatment of cancer will remain in L01BA01.

2) Existing ATC code B02BD04 coagulation factor IX

*Change of ATC level names:*

Previous	New	ATC code
atenolol and other antihypertensives	atenolol and nifedipine	C07FB03
Beta blocking agents and other antihypertensives	Beta blocking agents, other combinations	C07F
Beta blocking agents, selective, and other antihypertensives	Beta blocking agents and calcium channel blockers	C07FB
bisoprolol and other antihypertensives	bisoprolol and amlodipine	C07FB07
nebivolol and other antihypertensives	nebivolol and amlodipine	C07FB12
oxycodone, combination	oxycodone and naloxone	N02AA55

*Change of ATC code and/or ATC level name based on new ATC 4<sup>th</sup> levels established*

Previous ATC code and level name		New ATC code and/or level name	
<b>C07FA</b>	<b>Beta blocking agents, non-selective, and other antihypertensives</b>	Deleted	
		<b>C07FX</b>	<b>Beta blocking agents, other combinations</b>
<b>C07FA05</b>	propranolol and other antihypertensives	C07FX01	propranolol and other combinations
<b>C07AA57</b>	sotalol, combinations	C07FX02	sotalol and acetylsalicylic acid
<b>C07AB52</b>	metoprolol, combinations	C07FX03	metoprolol and acetylsalicylic acid
<b>C07FB02</b> <sup>1)</sup>	metoprolol and other antihypertensives	C07FB02 C07FB13	metoprolol and felodipine <sup>2)</sup> metoprolol and amlodipine
<b>C07AB57</b>	bisoprolol, combinations	C07FX04	bisoprolol and acetylsalicylic acid
		<b>N02AJ</b>	<b>Opioids in combination with non-opioid analgesics</b>
<b>N02AA58</b> <sup>3)</sup> <b>N02BE51</b> <sup>3)</sup>	dihydrocodeine, combinations paracetamol, combinations excl. psycholeptics	N02AJ01 <sup>4)</sup>	dihydrocodeine and paracetamol
<b>N02AA58</b> <sup>3)</sup> <b>N02BA51</b> <sup>3)</sup>	dihydrocodeine, combinations acetylsalicylic acid, combinations excl. psycholeptics	N02AJ02 <sup>4)</sup>	dihydrocodeine and acetylsalicylic acid
<b>N02AA58</b> <sup>3)</sup>	dihydrocodeine, combinations	N02AJ03 <sup>4)</sup>	dihydrocodeine and other non-opioid analgesics
<b>N02AA59</b> <sup>3)</sup> <b>N02BE51</b> <sup>3)</sup>	codeine, combinations excl. psycholeptics paracetamol, combinations excl. psycholeptics	N02AJ06 <sup>4)</sup>	codeine and paracetamol

/Continued

Change of ATC code and/or ATC level name based on new ATC 4<sup>th</sup> levels established, continued/

Previous ATC code and level name	New ATC code and/or level name
<b>N02AA59</b> <sup>3)</sup> codeine, combinations excl. psycholeptics	<b>N02AJ07</b> <sup>4)</sup> codeine and acetylsalicylic acid
<b>N02BA51</b> <sup>3)</sup> acetylsalicylic acid, combinations excl. psycholeptics	
<b>N02AA59</b> <sup>3)</sup> codeine, combinations excl. psycholeptics	<b>N02AJ08</b> <sup>4)</sup> codeine and ibuprofen
<b>M01AE51</b> <sup>3)</sup> ibuprofen, combinations	
<b>N02AA59</b> <sup>3)</sup> codeine, combinations excl. psycholeptics	<b>N02AJ09</b> <sup>4)</sup> codeine and other non-opioid analgesics
<b>N02AX52</b> tramadol, combinations	<b>N02AJ13</b> tramadol and paracetamol
<b>N02AA55</b> <sup>3)</sup> oxycodone, combinations <sup>5)</sup> paracetamol, combinations excl. psycholeptics	<b>N02AJ17</b> <sup>4)</sup> oxycodone and paracetamol
<b>N02BE51</b> <sup>3)</sup>	
<b>N02AA55</b> <sup>3)</sup> oxycodone, combinations <sup>3)</sup>	<b>N02AJ18</b> <sup>4)</sup> oxycodone and acetylsalicylic acid
<b>N02BA51</b> <sup>3)</sup> acetylsalicylic acid, combinations excl. psycholeptics	
<b>N02AA55</b> <sup>3)</sup> oxycodone, combinations <sup>3)</sup>	<b>N02AJ19</b> <sup>4)</sup> oxycodone and ibuprofen

1) Splitting of ATC code in connection with alterations in C07FX

2) Existing ATC code

3) Splitting of ATC codes according to contents of the different fixed combinations of opioids and other analgesics. The ATC codes in N02AA, N02BA51, N02BE51 and M01AE51 will be maintained for other combinations.

4) Combinations with opioids and other analgesics currently classified in the following ATC codes N02AA55, N02AA58, N02AA59 will be moved to the new ATC 4<sup>th</sup> level N02AJ. All the existing combination codes will be kept in N02AA since there may be other combinations without analgesics available (e.g. oxycodone and naloxone will remain in N02AA55). The ATC classification of all low dose combinations products of codeine or dihydrocodeine (<20 mg dose) currently classified in N02B or M01A will be altered to the new ATC codes in N02AJ.

5) Combinations of oxycodone and naloxone will be maintained in N02AA55.

**New DDDs:**

ATC level name/INN	DDD	unit	Adm.R*	ATC code
alirocumab	5.4	mg	P	C10AX14
apremilast	60	mg	O	L04AA32
ataluren	2.8	g	O	M09AX03
calcium acetate	6	g	O	V03AE07
cangrelor	50	mg	P	B01AC25
defibrotide	1.75	g	P	B01AX01
edoxaban	60	mg	O	B01AF03
elosulfase alfa	20	mg	P	A16AB12
evolocumab	14	mg	P	C10AX13
ferric citrate	6	g	O	V03AE08
furazidin	0.3	g	O	J01XE03
iloperidone	18	mg	O	N05AX14
insulin degludec and liraglutide	40	U <sup>1)</sup>	P	A10AE56
mifepristone, combinations	0.2	g <sup>2)</sup>	O	G03XB51
naloxegol	25	mg	O	A06AH03
rifapentine	0.11	g	O	J04AB05
safinamide	75	mg	O	N04BD03
secukinumab	10	mg	P	L04AC10
tedizolid	0.2	g	O,P	J01XX11

\* Administration Route: O=oral; P=parenteral

1) Refers to insulin degludec

2) Refers to mifepristone

**Change of DDD:**

ATC level name/INN	Previous DDD			New DDD			ATC code
	DDD	Unit	Adm.R.*	DDD	Unit	Adm.R.*	
Blood coagulation factors	<sup>1)</sup>			Deleted <sup>1)</sup>			B02BD
mifepristone	0.6	g	O	0.2	g	O	G03XB01
ampicillin and enzyme inhibitor	2	g <sup>2)</sup>	P	6	g <sup>2)</sup>	P	J01CR01

\* Administration Route: O=oral; P=parenteral

1) DDDs for the various blood coagulation factors in all ATC 5<sup>th</sup> level codes in B02BD are deleted. No new DDDs will be established in B02BD Blood coagulation factors.

2) Refers to ampicillin

## ATC/DDD classification (final)

The following ATC codes, DDDs and alterations were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in March 2015. These are considered as final and will be included in the January 2016 version of the ATC/DDD Index.

### New ATC 5<sup>th</sup> level codes:

ATC level name/INN	ATC code
anthrax immunoglobulin	J06BB19
armodafinil	N06BA13
atorvastatin, amlodipine and perindopril	C10BX11
begelomab	L04AA35
brexpiprazole	N05AX16
brodalumab	L04AC12
cediranib	L01XE32
ceftazidime, combinations	J01DD52
conjugated estrogens and bazedoxifene	G03CC07
drisapersen	M09AX04
droxidopa	C01CA27
dulaglutide	A10BX14
emtricitabine, tenofovir alafenamide and rilpivirine	J05AR19
ibuprofen	R02AX02
idarucizumab	V03AB37
ivacaftor and lumacaftor	R07AX30
ixazomib	L01XX50
lesinurad	M04AB05
necitumumab	L01XC22
palbociclib	L01XE33
pantoprazole, amoxicillin, clarithromycin and metronidazole	A02BD11
perindopril and bisoprolol	C09BX02
ramucirumab	L01XC21
reslizumab	R03DX08
salmeterol and budesonide	R03AK12
saxagliptin and dapagliflozin	A10BD21
selexipag	B01AC27
sodium benzoate	A16AX11
tivozanib	L01XE34
valsartan and lercanidipine	C09DB08
valsartan and sacubitril	C09DX04
zoledronic acid, calcium and colecalciferol, sequential	M05BB08

### Change of ATC codes:

ATC level name/INN	Previous ATC code	New ATC code
calcium acetate <sup>1)</sup>	A12AA12	V03AE07
ferric citrate	B03AB06	V03AE08

<sup>1)</sup> Previous ATC level name: calcium acetate anhydrous

**New DDDs:**

ATC level name/INN	DDD	unit	Adm.R*	ATC code
alogliptin	25	mg	O	A10BH04
armodafinil	0.15	g	O	N06BA13
artesanate	0.28	g	P	P01BE03
clenbuterol	40	mcg	O	R03CC13
colistin	3	MU	Inhal. powder	J01XB01
dasabuvir	0.5	g	O	J05AX16
dulaglutide	0.16	mg	P	A10BX14
eliglustat	0.168	g	O	A16AX10
empagliflozin	17.5	mg	O	A10BX12
teduglutide	5	mg	P	A16AX08
tofacitinib	10	mg	O	L04AA29
umeclidinium bromide	55	mcg <sup>2</sup>	Inhal. powder	R03BB07

\* Administration Route: O=oral; P=parenteral

<sup>2)</sup> Refers to umeclidinium, delivered dose

**Change of DDDs:**

ATC level name/INN	Previous DDD			New temporary DDD			ATC code
	DDD	unit	Adm.R*	DDD	unit	Adm.R*	
apixaban	5	mg	O	10	mg	O	B01AF02
dabigatran etexilate	0.22	g	O	0.3	g	O	B01AE07
human menopausal gonadotrophin	30	U	P	75	U	P	G03GA02
rivaroxaban	10	mg	O	20	mg	O	B01AF01

\* Administration Route: O=oral; P=parenteral