WHO Drug Information

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International Conference of Drug Regulatory Authorities (ICDRA)

The 16th ICDRA will be hosted by the Brazilian National Health Surveillance Agency (ANVISA)

Rio de Janeiro, Brazil
24 — 29 August 2014

http://www.anvisa.gov.br
Quality and Safety of Medicines

Falsified lamivudine/zidovudine/nevirapine tablets: rapid identification using X-ray fluorescence technique

The X-ray fluorescence (XRF) technique was used to determine bromine (Br) concentration in lamivudine/zidovudine/nevirapine (Zidolam-N®) tablets from fourteen batches drawn from different sources. Results showed that Br concentration in falsified drugs was significantly higher than that in the authentic drugs. It was also found that Br concentration in the paper liner of the bottle caps containing the falsified drugs was elevated when compared to the liner from the container holding the authentic drug. In conclusion, falsified (Zidolam-N®) can be rapidly identified using the handheld, portable XRF instrument.

On 22 September 2011, the World Health Organization (WHO) announced the discovery of falsified Zidolam-N® tablets in Kenya. These were labelled as manufactured and supplied by Hetero, India (batch No. E100766). Later, medicines labelled as Hetero batches A9351, A9366 and E110467 were also confirmed to be falsified. Hetero further declared that batches E100766 and E110467 were never supplied to Kenya and that the quantities declared as batches A9351, A9357 and A9366 exceeded those actually manufactured. Falsified medicines labelled as batches A9366 and E100766 were sent to the Kenya National Drug Quality Control Laboratory and to Hetero for examination.

The test results were not conclusive in tracking the source of the falsification. Given this situation, WHO requested the China National Institutes for Food and Drug Control (NIFDC) to develop a rapid detection method to differentiate the authentic from the falsified medicines. The following is a description of testing methods and results.

Instrument used
Thermo Scientific Model Nition XL3t XRF Analyzer®. Manufacturer: Thermo NITION Analyzen LLC.Model:XL3t970.Serial:82321.

Testing Method

Instrument setting
Plastic mode, 50 kV excitation voltage, main filter measurement time set to 60s, error of measurement display set to ±1σ standard deviation (68.3% confidence).

Tablet testing
Six tablets were randomly taken from each sample batch. For each test, two tablets were used and three tests were performed for one batch and tests were repeated the next day.
Sample Information

<table>
<thead>
<tr>
<th>Sample source</th>
<th>Batch No.</th>
<th>Sample No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya, transferred to WHO (Original package with bottle)</td>
<td>A9366</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>E100766</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>E110467</td>
<td>C</td>
</tr>
<tr>
<td>Kenya (Nude tablets without bottle)</td>
<td>A9366</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>E100766</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>E110467</td>
<td>F</td>
</tr>
<tr>
<td>Hetero, India (Nude tablets without bottle)</td>
<td>A9366</td>
<td>G</td>
</tr>
<tr>
<td></td>
<td>E100766</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>E110467</td>
<td>I</td>
</tr>
<tr>
<td>Hetero, India Control sample not for sale (Original package with bottle)</td>
<td>A9351</td>
<td>J</td>
</tr>
<tr>
<td></td>
<td>A9357</td>
<td>K</td>
</tr>
<tr>
<td>WHO (originated Kenya) (Original package with bottle)</td>
<td>A9366</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td>E100766</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>E110467</td>
<td>N</td>
</tr>
</tbody>
</table>

Packaging material

The bottle bottoms, bottle caps and the paper cap liner were determined.

Optimization of testing conditions

Testing conditions for bromine in tablets (*See tables 1 and 2*)

*Condition a*

Instrument setting: Plastic mode, thickness correction enabled, main filter set to 60s measurement time, error of measurement set to display ±1σ standard deviation.

*Condition b*

Instrument setting: Plastic mode, thickness correction disabled, main filter set to 60s measurement time, error of measurement set to display ±2σ standard deviation (95.5% confidence).

*Condition c*

Instrument setting: Plastic mode, thickness correction disabled, main filter set to 90s measurement time, error of measurement set to display ±1σ standard deviation.

Results

Results of the packaging materials of samples tested are shown in Table 3.
Table 1. Results of tablet samples tested

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Measured concentration of Br (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Condition a</td>
</tr>
<tr>
<td>A</td>
<td>13±1</td>
</tr>
<tr>
<td>B</td>
<td>20±1</td>
</tr>
<tr>
<td>C</td>
<td>34±1</td>
</tr>
<tr>
<td>D</td>
<td>16±1</td>
</tr>
<tr>
<td>E</td>
<td>14±1</td>
</tr>
<tr>
<td>F</td>
<td>8±1</td>
</tr>
<tr>
<td>G</td>
<td>&lt;3</td>
</tr>
<tr>
<td>H</td>
<td>&lt;3</td>
</tr>
<tr>
<td>I</td>
<td>&lt;3</td>
</tr>
<tr>
<td>J</td>
<td>&lt;3</td>
</tr>
<tr>
<td>K</td>
<td>&lt;3</td>
</tr>
<tr>
<td>L</td>
<td>12±1</td>
</tr>
<tr>
<td>M</td>
<td>71±1</td>
</tr>
<tr>
<td>N</td>
<td>44±1</td>
</tr>
</tbody>
</table>

Table 2. Results of tablet samples tested on different days

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Br (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td>A</td>
<td>17±1</td>
</tr>
<tr>
<td>B</td>
<td>24±1</td>
</tr>
<tr>
<td>C</td>
<td>43±1</td>
</tr>
<tr>
<td>D</td>
<td>19±1</td>
</tr>
<tr>
<td>E</td>
<td>17±1</td>
</tr>
<tr>
<td>F</td>
<td>9±1</td>
</tr>
<tr>
<td>G</td>
<td>&lt;3</td>
</tr>
<tr>
<td>H</td>
<td>&lt;3</td>
</tr>
<tr>
<td>I</td>
<td>&lt;3</td>
</tr>
<tr>
<td>J</td>
<td>&lt;3</td>
</tr>
<tr>
<td>K</td>
<td>&lt;3</td>
</tr>
<tr>
<td>L</td>
<td>17±1</td>
</tr>
<tr>
<td>M</td>
<td>89±1</td>
</tr>
<tr>
<td>N</td>
<td>57±1</td>
</tr>
</tbody>
</table>
Discussion

As seen from the data reported, Br concentrations detected in samples A, B, C, D, E, F, L, M and N are much higher than those in samples G, H, I, J and K which are below the instrument detection limit.

Note: When the instrument is set in plastic mode and the total testing time on the main filter is 30s, the detection limit for Br is 3 ppm.

Instrument repeatability was good.

Relative average deviations of the test results on the two consecutive days are all smaller than 6%.

Br was not detected in inner packages of samples D, E, F, G, H and I.

Br was not detected in the bottom, cap, and side wall of the plastic bottles containing samples A, B, C, J, K, L, M and N.

Br was not detected in the paper liner of the bottle cap of control samples J and K. However, the levels of Br detected in the paper liner of the bottle cap of suspected counterfeit samples A, B, C, L, M and N is relatively high.

Conclusion

An XRF technique was successfully used for rapid and non-destructive measurement of Br concentration in samples of tablets of medicines. A handheld XRF instrument employed in this study is simple to use and offers good repeatability and sensitivity for Br in medicinal drugs. It is suitable for rapid, positive authentication of lamivudine/zidovudine/nevirapine (Zidolam-N®) tablets using Br measurement as an indicator.
References


Safety and Efficacy Issues

Rituximab: hepatitis B reactivation

Canada — Health Canada has informed healthcare professionals of updates to the recommendations for screening and management of hepatitis B virus reactivation in patients treated with rituximab (Rituxan®).

Rituximab is an anti-CD20 monoclonal antibody indicated in the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (also known as Wegener granulomatosis) and microscopic polyangiitis.

Use of rituximab has been shown to be associated with reactivation of hepatitis B virus in seropositive patients. It is advised that all patients be screened for hepatitis B virus (HBV) before initiation of treatment. Rituximab is not to be used in patients with active hepatitis B viral disease.

Prior to starting treatment in HBV seropositive patients, consultation with a liver disease expert is recommended to determine ongoing monitoring of HBV reactivation and its management.

The use of rituximab has been associated with HBV reactivation in patients with positive HBV surface antigen (HBsAg+ve) and in those with negative HBV surface antigen plus positive anti-HB core antibody (HBsAg-ve/HBcAb+ve), particularly when administered in combination with corticosteroids or chemotherapy.


Oral fluoroquinolones and retinal detachment

Canada — Oral fluoroquinolones are broad-spectrum antibacterial drugs indicated for the treatment of infections caused by susceptible strains of microorganisms (1–5). In Canada, there are five marketed oral fluoroquinolones: ciprofloxacin (first marketed in 1996), levofloxacin (1997), moxifloxacin (2000), norfloxacin (1986), and ofloxacin (1990). The risk of retinal detachment is not described in any of the oral fluoroquinolone Canadian product monographs.

Retinal detachment is a serious medical emergency that generally requires prompt surgical intervention (6, 7). According to a pharmacoepidemiological study, current use of oral fluoroquinolones was associated with an increased risk of developing retinal detachment (7). Ophthalmic fluoroquinolones were excluded from the study to avoid reverse causality bias. The study identified 445 cases of retinal detachment involving oral fluoroquinolone use in a cohort of 989 591 patients from British Columbia.
who visited an ophthalmologist between January 2000 and December 2007. Further research is needed to confirm whether there is a potential association between retinal detachment and fluoroquinolones as well as to clarify the mechanism of action.

As of 31 December 2012, Health Canada received one report of retinal detachment suspected of being associated with the use of an oral fluoroquinolone. The report described a 52-year-old woman who experienced retinal detachment after a course of ciprofloxacin prescribed to treat a bladder infection. Limited evidence linking retinal detachment to oral fluoroquinolones may explain the low level of reporting to Health Canada.

Extracted from the Canadian Adverse Drug Reactions Newsletter, Volume 23, number 3, 2013.

References


Hydroxyethyl starch solutions: kidney failure

Canada — Health Canada has informed healthcare professionals of updated information concerning blood volume expanders containing hydroxyethyl starch (HES) solutions recommending that these products no longer be used in critically ill patients with certain health conditions.

HES solutions are used to replace lost blood in patients who are critically ill and experience a sudden drop in blood pressure.

Specifically, HES solutions should not be used:

- In patients with sepsis.
- In patients with severe liver disease.
- In certain types of patients with impaired kidney function.

Some recent studies have compared HES with other blood volume expanders in critically ill patients with sepsis. These studies suggest that patients treated with HES are at a higher risk of kidney failure or death.


Ketoconazole: fatal liver injury

United States of America — The Food and Drug Administration (FDA) is taking several actions related to ketoconazole (Nizoral®) oral tablets. These include limiting use, warning of severe liver injuries and adrenal gland problems and advising that it can lead to harmful drug interactions with other medications.

The FDA has approved label changes and added a new medication guide to address these safety issues. As a result, ketoconazole oral tablets should not be considered as first-line treatment for any
Safety and Efficacy Issues

fungal infection. Ketoconazole should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated.

Topical formulations of ketoconazole have not been associated with liver damage, adrenal problems, or drug interactions.

Ketoconazole tablets can cause liver injury, which may potentially result in liver transplantation or death. Serious liver damage has occurred in patients receiving high doses of ketoconazole for short periods of time as well as those receiving low doses for long periods. Some of these patients had no obvious risk factors for liver disease.

Ketoconazole tablets may cause adrenal insufficiency and healthcare professionals should monitor adrenal function in patients who have existing adrenal problems or in patients who are under prolonged periods of stress such as those who have had a recent major surgery or who are under intensive care in the hospital. Ketoconazole tablets may interact with other drugs and result in serious and potentially life-threatening outcomes.


Olmesartan medoxomil: enteropathy

United States of America — The Food and Drug Administration (FDA) is warning that the blood pressure drug olmesartan medoxomil (Benicar®, Benicar HCT®, Azor®, Tribenzor®, and generics) can cause sprue-like enteropathy.

Symptoms include severe, chronic diarrhoea with substantial weight loss. The enteropathy may develop months to years after starting olmesartan, and sometimes requires hospitalization. If patients taking olmesartan develop these symptoms and no other cause is found, the drug should be discontinued, and therapy with another antihypertensive started.

Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) approved for the treatment of high blood pressure, alone or with other antihypertensive agents, and is one of eight marketed ARB drugs. Sprue-like enteropathy has not been detected with ARB drugs other than olmesartan.


Ado-trastuzumab emtansine: name confusion

United States of America — The Food and Drug Administration (FDA) is alerting healthcare professionals that the use of the incorrect nonproprietary name for the breast cancer drug ado-trastuzumab emtansine (Kadcyla®) in some medication-related electronic systems poses a risk of mix-up with trastuzumab (Herceptin®) and may result in medication errors. The dosing and treatment schedules for ado-trastuzumab emtansine and trastuzumab, another breast cancer drug, are quite different, so confusion between these products could lead to dosing errors and potential harm to patients.

The FDA-approved nonproprietary name ado-trastuzumab emtansine should be used. However, some third-party publications, compendia references, health information systems (e.g., electronic health record systems and systems used for pharmacy prescription processing, wholesaler ordering, pharmacy ordering, etc.) and sites on the Internet are incorrectly using the United States Adopted Name (USAN), which is “trastuzumab emtansine,” and omitting the “ado” prefix and hyphen. Use of this truncated version may cause confusion.
It is important for drug information content publishers to identify drug products by the FDA-approved proprietary (brand) and nonproprietary names that are used in FDA-approved drug labels.


Anticholinergics and cognitive impairment

Australia — Anticholinergics are a class of drug that blocks muscarinic actions of acetylcholine with a wide range of effects. Drugs with definite anticholinergic properties include antiemetics (promethazine®), anti-Parkinson agents (benztropine), gastrointestinal spasmolytics (propantheline), bladder spasmalytics (oxybutinin, tolterodine) and anti-depressants (imipramine) (1).

Precautions for anticholinergics include using with caution in elderly patients who are more sensitive to adverse events associated with these drugs. In particular, confusion can be precipitated or worsened. When used in elderly patients, anticholinergics should be initiated at a low dose and increased slowly to the lowest effective dose.

Two recent long-term studies examined cognitive impairment in older patients.

One of those studies followed 13 004 patients aged 65 and older for two years (2). The other study followed 1652 African American subjects over 70 years of age, for six years (3). These patients experienced a 1.43 times increased risk of developing cognitive impairment compared to patients not taking a drug with definite anticholinergic properties. Also, the risk increased with the number of anticholinergics being used.

Consideration should be given to routine measurement of cognitive function in older patients taking drugs with anticholinergic properties for any indication, including non-nervous system indications. It may be possible to lower the anticholinergic burden by replacing such drugs with alternatives that do not have anticholinergic properties.


References


Diclofenac : new safety advice

European Union — The Coordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh) has endorsed new safety advice for diclofenac-containing medicines in the form of capsules, tablets, suppositories or injections. The new advice aims to minimize cardiovascular risk.

This follows a recent review by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC), which found that the effects of systemic diclofenac are similar to those of selective COX-2 inhibitors particularly when diclofenac is used at a high dose and for long-term treatment. The PRAC therefore recommended that the same precautions already in place should be applied to diclofenac.
Clinical-trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events associated with the use of diclofenac, particularly at high dose (150 mg daily) and in long-term treatment.

Use of diclofenac is contraindicated in patients with established congestive heart failure, ischaemic heart disease, peripheral arterial disease or cerebrovascular disease.

Patients with significant risk factors for cardiovascular events (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.

References


New recommendations for intravenous iron-containing medicines

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has completed its review of intravenous iron-containing medicines used to treat iron deficiency and anaemia associated with low iron levels. The CHMP concluded that the benefits of these medicines are greater than their risks, provided that adequate measures are taken to minimize the risk of allergic reactions.

All intravenous iron medicines have a small risk of causing allergic reactions which can be life-threatening if not treated promptly. The Committee therefore concluded that Iron preparations should only be given in an environment where resuscitation facilities are available. In addition, a test dose is no longer recommended but instead caution is warranted with every dose of intravenous iron that is given, even if previous administrations have been well tolerated.

The CHMP also considered that intravenous iron medicines should not be used during pregnancy unless clearly necessary. Treatment should be confined to the second or third trimester, provided the benefits of treatment clearly outweigh the risks to the unborn baby.

The review of intravenous iron medicines was triggered by the French medicines agency, the National Agency for the Safety of Medicine and Health Products (ANSM)


Vemurafenib: DRESS syndrome

Singapore — Healthcare professionals have been informed of the risk of RAS-mutant malignancy progression and DRESS syndrome associated with vemurafenib (Zelboraf®). The risk of RAS-mutant malignancy progression is based on a single report from a literature article about a 76 year-old male patient with stage IV melanoma in whom accelerated growth of a pre-existing NRAS-mutated chronic myelomonocytic leukemia (CMML) was observed shortly after initiation of treatment with
vemurafenib. Based on its mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations. Vemurafenib should be used with caution in patients with prior or concurrent cancers associated with RAS mutations.

In addition, cases of DRESS syndrome have been reported with the use of vemurafenib with onset ranging from 7 to 25 days. Treatment should be permanently discontinued if a patient develops DRESS syndrome. The package insert for Zelboraf® will be updated to reflect the new safety information.


Mefloquine: risk of neurological and psychiatric effects

United States of America — The Food and Drug Administration (FDA) is advising the public about strengthened and updated warnings regarding neurologic and psychiatric side effects associated with the antimalarial drug mefloquine hydrochloride.

Neurological side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include feeling anxious, mistrustful, depressed, or having hallucinations.

Neurological side effects can occur at any time during drug use and can last for months to years after the drug is stopped, or can be permanent.


Calcitonin: changes to availability

Canada — Health Canada has advised of important changes to the availability and recommended conditions of use of drugs containing calcitonin. Calcitonin is used as a nasal spray to treat osteoporosis in postmenopausal women, and as an injection to treat Paget disease and hypercalcaemia.

A safety review conducted by Health Canada has concluded that there is a slightly increased risk of cancer associated with prolonged use. A review of the benefits and risks of the nasal spray products found that there was not enough evidence of benefit to continue using calcitonin nasal sprays in treating osteoporosis.

As a result of these reviews, calcitonin nasal spray products will no longer be authorized for sale in Canada as of 1 October 2013.


Mefloquine: risk of eye disorders

Singapore — Healthcare professionals have been informed of an increased risk of eye disorders including cataract, retinal disorders and optic neuropathy during or after treatment with mefloquine (Lariam®). These eye disorders can present with visual impairment and blurred vision. Increased risk of eye disorders is based on outcomes of a review of available evidence from non-clinical studies, the Roche global drug safety database and published literature.

Adverse events may occur or persist up to several weeks after discontinuation of Lariam® due to the long half-life of the drug. The package insert will be updated to reflect the new safety information.

Calcitonin injectable products will continue to be authorized for sale in Canada. The benefits of these products are considered to outweigh the risks when the product is used as directed. However, the labels for calcitonin injectable products are being updated to include a new warning and to recommend that treatment with calcitonin solution for injection be limited to the shortest possible time, using the minimum effective dose. Treatment of symptomatic Paget disease with calcitonin medicine should be limited to patients who are unable to use other treatments.


Metoclopramide: changes to use

European Union — The European Medicines Agency’s Committee on Medicinal Products for Human Use (CHMP) has recommended changes to the use of metoclopramide-containing medicines, including restricting the dose and duration of use to minimize the known risks of potentially serious neurological side effects.

Metoclopramide-containing medicines have been authorized separately in individual Member States with differing licensed indications such as nausea and vomiting or gastrointestinal motility disorders.

The review of metoclopramide was carried out at the request of the French medicines regulatory agency (ANSM), following continued safety concerns over side effects and concerns over efficacy. The review confirmed the known risks of neurological effects such as short-term extrapyramidal disorders. The risk of acute neurological effects is higher in children, although tardive dyskinesia is reported more often in the elderly, and the risk is increased at high doses or with long-term treatment. The evidence indicated that these risks outweighed the benefits of metoclopramide in conditions requiring long-term treatment. There have also been very rare cases of serious effects on the heart or circulation, particularly after injection.

The Committee recommended that metoclopramide should only be prescribed for use up to five days, that it should not be used in children below one year of age and that in children over one year of age, it should only be used as a second-choice treatment for the prevention of delayed nausea and vomiting after chemotherapy and for the treatment of post-operative nausea and vomiting.

In adults, it may be used for the prevention and treatment of nausea and vomiting such as that associated with chemotherapy, radiotherapy, surgery and in the management of migraine. In addition, the maximum recommended doses in adults and children should be restricted, and higher strength formulations removed from the market.


Glucagon-like-peptide-1 therapies: no immediate concern

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has finalized a review of GLP-1-based diabetes therapies. The Committee concluded that presently available data do not confirm recent concerns over an increased risk of pancreatic adverse events with these medicines.

The rise of type-2 diabetes is a major public-health challenge. GLP-1-based therapies are effective treatments for type-2 diabetes and add to the available medication options. The term...
‘GLP-1-based therapies’ comprises two classes of medicines: glucagon-like-peptide-1 (GLP-1) agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors.

A review was initiated following publication of a study that suggested an increased risk of pancreatitis and pancreatic-duct metaplasia in patients with type-2 diabetes treated with GLP-1-based therapies. Following the review of the publication and consultation of a panel of experts, the CHMP considered that the study itself had a number of methodological limitations which preclude a meaningful interpretation of the results.

These medicines already carry warnings in their product information but the CHMP considered that there would be value in harmonizing the wording to provide consistent advice.

Two large independent studies funded by the European Commission have been under way since 2011 to study the risk profile of diabetes treatments in general. First results of these studies are expected in 2014.

References


Ergot derivatives: restricted use

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended restricting the use of medicines containing ergot derivatives. These medicines should no longer be used to treat several conditions involving blood circulation problems or problems with memory and sensation, or to prevent migraine headaches, since the risks are greater than the benefits in these indications. A review of data showed an increased risk of fibrosis and ergotism.

Ergot derivatives indicated for these conditions will have their marketing authorizations suspended. In some EU Member States, ergot derivatives are also authorized for other indications: dementia, including Alzheimer disease, and treatment of acute migraine headache. They will remain authorized for use in those indications.

The review was initiated due to concerns identified by the French National Agency for the Safety of Medicine and Health Products (ANSM) in a national pharmacovigilance review in 2011.

Fibrosis can be a serious, sometimes fatal disease. The CHMP noted that there is a plausible mechanism by which ergot derivatives could cause fibrosis and ergotism. Given that the evidence for benefit in these indications was very limited, the CHMP concluded that the benefits in the concerned indications did not outweigh the risk of fibrosis and ergotism.


Flupirtine-containing medicines: restricted use

European Union — The Coordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh) has endorsed new recommendations to restrict the use of oral flupirtine medicines and suppositories. These medicines should now only be used for treating acute pain in adults who cannot use other painkillers, such as non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids and...
treatment should not last longer than two weeks.

Patient liver function should be checked after each full week of treatment and treatment should be stopped if the patient has any signs of liver problems. Flupirtine must also not be used in patients with pre-existing liver disease or alcohol abuse problems or in patients taking other medicines known to cause liver problems.

The recommendations follow a review by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC). In addition to oral medicines and suppositories, the review also covered injectable flupirtine medicines which were being given as a single injection for pain following surgery. The PRAC concluded that the benefits of injectable flupirtine continue to outweigh their risks when used in this way.

Flupirtine is a non-opioid used to treat pain, such as that associated with muscle tension, cancer, menstrual and pain following orthopaedic surgery or injuries. It was first introduced as an alternative painkiller to opioids and NSAIDs. Subsequently, multiple other actions such as muscle relaxation were identified. Flupirtine works as a selective neuronal-potassium-channel opener.


Interim guidelines on bedaquiline for tuberculosis

The World Health Organization has issued interim guidance on the use of the anti-TB medicine, bedaquiline, which received accelerated approval by the US Food and Drug Administration on 31 December 2012. In view of the urgent need to combat multidrug-resistant TB (MDR-TB) with improved drugs, WHO has provided recommendations based on clinical trial data.

The MDR-TB epidemic registered 310 000 new cases in 2011. However, only 19% of people thought to be infected are receiving some kind of treatment. It is hoped that bedaquiline — which has been shown in trials to be potentially effective against *Mycobacterium tuberculosis* — could become a powerful tool in much-needed treatment regimens that will be significantly shorter, more effective and less toxic than the current regimen which involves a two-year course of up to 20 pills per day and eight months of daily injections.


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

Operation Pangea VI: combating sale of unapproved medicines

United States of America — The Food and Drug Administration and international regulatory and law enforcement agencies have taken action against more than 9600 web sites that illegally sell potentially dangerous, unapproved prescription medicines to consumers. This action includes issuance of regulatory warnings and seizure of offending web sites and over 41 million US dollars’ worth of illegal medicines worldwide. The action occurred as part of the 6th annual International Internet Week of Action (IIWA), a global cooperative effort to combat the online sale and distribution of potentially counterfeit and illegal medical products. The goal of Pangea VI — which involves law enforcement, customs, and regulatory authorities from 99 countries — was to identify the makers and distributors of illegal drug products and medical devices and remove these products from the supply chain.

As part of this international effort, the FDA Office of Criminal Investigations, in coordination with the United States Attorney’s Office for the District of Colorado, seized and shut down 1677 illegal pharmacy web sites. The effort ran from 18–25 June 2013.

Many of these web sites appeared to be operating as a part of an organized criminal network that falsely purported to be “Canadian Pharmacies.” These web sites displayed fake licences and certifications to convince U.S. consumers to purchase drugs they advertised as “brand name” and “FDA approved.” The drugs collected as part of Operation Pangea were not from Canada, and were neither brand name nor FDA approved. These web sites also used certain major U.S. pharmacy retailer names to trick consumers into believing an affiliation existed.


SARA: System for Australian Recall Actions

Australia — The Therapeutic Goods Administration (TGA) recently launched the System for Australian Recall Actions (SARA) — an online, searchable data base of recall actions for therapeutic goods undertaken in Australia.

Health professionals are encouraged to use SARA, along with other resources on the TGA website, such as the Database of Adverse Event Notifications and the alerts web page, to access valuable information on medicines safety.

A recall action is a regulatory action taken for a therapeutic good supplied in Australia to resolve issues or deficiencies relating to safety, quality, efficacy or performance. Recall actions can be recalls, recalls for product correction or hazard alerts. Not all recall actions result in a product being removed from the market, for example hazard alerts may be issued in cases involving implantable devices, and corrections may be undertaken for products that have software issues.

SARA includes recall actions for a range of therapeutic goods including prescription medicines, over-the-counter medicines, complementary medicines, medical devices including
in vitro diagnostic medical devices, and biologicals.

The data base holds information on all recall actions that have been undertaken in Australia since 1 July 2012.

SARA has been launched as part of the TGA’s commitment to improve transparency, as well as trust and confidence in the safety and quality of therapeutic goods and regulatory processes.


Oral ketoconazole: suspension of marketing authorization

European Union — The European Medicines Agency’s Committee on Medicinal Products for Human Use (CHMP) has recommended that the marketing authorizations of oral ketoconazole-containing medicines should be suspended throughout the European Union (EU). The CHMP concluded that the risk of liver injury is greater than the benefits in treating fungal infections.

Patients currently taking oral ketoconazole for fungal infections should make a non-urgent appointment with their doctor to discuss suitable alternative treatments. Doctors should no longer prescribe oral ketoconazole and should review treatment options.

The EU-wide review of oral ketoconazole was triggered by the suspension of the medicine in France. Having assessed the available data, the CHMP concluded that liver injury with oral ketoconazole was higher than with other antifungals. The CHMP was concerned that reports of liver injury occurred early after starting treatment with recommended doses and it was not possible to identify measures to adequately reduce this risk. The Committee also concluded that the clinical benefit of oral ketoconazole is uncertain as data on its effectiveness are limited and do not meet current standards, and alternative treatments are available.

Topical formulations of ketoconazole can continue to be used as the amount of ketoconazole absorbed throughout the body is very low with these formulations.

References


Advanced therapy approved for metastatic prostate cancer

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorization for a new advanced-therapy medicinal product (ATMP). Provenge® is recommended for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated.

ATMPs are innovative medicines that are derived from gene therapy, cell therapy or tissue engineering. The CHMP recommendation follows the draft opinion of the Committee for Advanced Therapies (CAT), the Agency’s expert committee for ATMPs.

Provenge® is a cellular immunotherapy designed to induce an immune response
against prostate cancer cells. It uses immune cells that are extracted from and treated outside the patient’s body so that when they are infused back into the patient they trigger an immune response directed against an antigen found in metastasized cancer cells. Provenge® has been shown to improve the overall survival by 4.1 months over placebo in clinical trials.


Calcitonin nasal spray: market withdrawal

Canada — Health Canada has advised of the market withdrawal of all synthetic calcitonin nasal spray products (Miacalcin®, Sandoz Calcitonin® and Apo-calcitonin®) with effect 1 October 2013. All three products are authorized in Canada for the treatment of post-menopausal osteoporosis in females five years post menopause with low bone mass relative to healthy pre-menopausal females.

Health Canada has concluded, in light of a newly identified risk of cancer, that the benefit-risk profile for the treatment of postmenopausal osteoporosis is no longer considered favourable. As of 3 July 2013, manufacturers have ceased the sale of synthetic calcitonin nasal spray products.


Afatinib and companion test approved for late-stage lung cancer

United States of America — The Food and Drug Administration (FDA) has approved afatinib (Gilotrif®) for patients with late stage (metastatic) non-small cell lung cancer (NSCLC) whose tumours express specific types of epidermal growth factor receptor (EGFR) gene mutations, as detected by an FDA-approved test.
Lung cancer is the leading cause of cancer-related death among men and women. About 85 percent of lung cancers are NSCLC, making it the most common type of lung cancer. EGFR gene mutations are present in about 10 percent of NSCLC, with the majority of these gene mutations expressing EGFR exon 19 deletions or exon 21 L858R substitution.

Afatinib is a tyrosine kinase inhibitor blocking proteins that promote the development of cancerous cells. It is intended for patients whose tumours express the EGFR exon 19 deletions or exon 21 L858R substitution gene mutations. Afatinib is being approved concurrently with the therascreen EGFR RGQ PCR Kit®, a companion diagnostic that helps determine if a patient’s lung cancer cells express the EGFR mutations.

In May 2013, the FDA approved erlotinib (Tarceva®) for first-line treatment of patients with NSCLC and a new indication was approved concurrently with the cobas EGFR Mutation Test® to identify patients with tumours expressing the EGFR gene mutations.

Common side effects of Gilotrif® include diarrhoea, skin breakouts that resemble acne, dry skin, pruritus, inflammation of the mouth, paronychia, decreased appetite, decreased weight, cystitis, nose bleed, runny nose, fever, eye inflammation and hypokalemia. Serious side effects include diarrhoea that can result in kidney failure and severe dehydration, severe rash, lung inflammation and liver toxicity.

Recent Publications, Information and Events

Priority medicines for Europe and the world

World Health Organization — For the first time, EU countries have more people over 65 years of age than under 15 years of age. Echoing the trend seen in Europe, much of the rest of the world is moving in a similar direction. Priority medicines for Europe and the world 2013 update calls for pharmaceutical researchers to adjust their research and development efforts to account for this shifting demography.

The report focuses on pharmaceutical gaps, where treatment for a disease or condition may soon become ineffective, are not appropriate for the target patient group, does not exist, or are not sufficiently effective. This report is an update to the 2004 version and is a collaborative product of experts from WHO, EU Member States, industry, academia and other interested stakeholders including patients.


HIV treatment recommendations

World Health Organization — The new WHO HIV treatment guidelines recommend offering antiretroviral therapy (ART) earlier. Recent evidence indicates that earlier ART will help people with HIV to live longer, healthier lives, and substantially reduce the risk of transmitting HIV to others.

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection encourage all countries to initiate treatment in adults living with HIV when their CD4 cell count falls to 500 cells/mm³ or less. WHO has based its recommendation on evidence that treating people with HIV earlier, with safe, affordable, and easier-to-manage medicines can both keep them healthy and lower the amount of virus in the blood, which reduces the risk of transmission.

The new recommendations also propose providing antiretroviral therapy to all HIV positive children under five years of age, pregnant and breastfeeding women with HIV, and all HIV-positive partners where one partner in the relationship is uninfected. WHO continues to recommend that all people with HIV with active tuberculosis or with hepatitis B disease receive antiretroviral therapy.

Another new recommendation is to offer all adults starting to take ART the same daily single fixed-dose combination pill. The recommended treatment is now a combination of three antiretroviral drugs: tenofovir and lamivudine (or emtricitabine) and efavirenz, as a single pill, given once daily.

If countries can integrate these changes within their national HIV policies, and back them up with the necessary resources, they will see significant health benefits at the public health and individual level. WHO is also encouraging countries to enhance the ways they deliver HIV services, for example by linking them more closely with other health sectors.

18th Model List of Essential Medicines and Model List for Children

World Health Organization — The 19th Expert Committee on Selection and Use of Essential Medicines met in April 2013 to review and update the WHO Model List of Essential Medicines and the List of WHO Essential Medicines for Children. The committee considered 52 applications and made 15 reviews.

The 18th WHO Model List of Essential Medicines and the 4th list of WHO Essential Medicines for Children was finalized by the Committee at the end of their deliberations.


• WHO Model List of Essential Medicines at http://www.who.int/entity/medicines/publications/essentialmedicines/18th_EML_Final_web_8Jul13.pdf and


International summit on medicines shortages

The International Pharmaceutical Federation (FIP) — a world federation of pharmacists and pharmaceutical scientists, recently convened an International summit on medicines shortages in Toronto, Canada.

While there has been considerable attention on the issue of medicines shortages in North America and in some European countries, there has been less attention given to the global reach of this ongoing crisis and to possible global responses.

The Summit was attended by 50 experts representing governments and regulatory authorities, the generic and innovative pharmaceutical industries, wholesalers, group purchasing organizations, pharmacists, various medicalspecialties, dentists and patient organizations. Input was also provided by the World Health Organization.

The Summit recommends that the following approaches should be investigated.

• In order to advance transparency and increase communication between all stakeholders on existing shortages, each country should establish a publicly accessible means of providing information. The mid to long term aim should be to aggregate this information at international level.

• A global process to determine a list of critical or vulnerable products should be developed. This would be most easily done by a multilateral organization. The list will require continuous revision and will inform regulatory responses, procurement practices and risk mitigation strategies. Each country could adapt the list to local conditions.

• All procurers of medicines are urged to move towards active procurement processes that assure the continuity of supply of quality medicines.

• All countries are encouraged to remove unnecessary variability of regulatory practices within and between countries.

• All regulatory authorities need to advance responsible transparency in relation to all regulatory processes.

• All countries should investigate the potential to establish a national body...
charged with gathering and sharing information about demand for and supply of medicines within their jurisdiction.

- All countries are encouraged to develop evidence-based risk mitigation strategies which might include strategic buffer stocks and stock piles, contingency planning, pandemic planning and capacity redundancy appropriate to their national needs.


**USAID Deliver Project: supply chain management**

The USAID Deliver Project has published the following new material:

*Alternative Public Health Supply Chains: Reconsidering the Role of the Central Medical Store* and *Getting Products to People Without a Traditional Central Medical Store*. The report and policy brief identify a set of approaches that either de-emphasize the Central Medical Store (CMS), or enacts a radical shift in management. These approaches potentially offer a superior solution to improving supply chain performance benefits compared to approaches that continue to emphasize the CMS. Available at http://j.mp/13HDMkG.

French and Spanish translations of the updated *Logistics Handbook: A Practical Guide for the Supply Chain Management of Health Commodities*. The *Logistics Handbook*, updated in 2011, offers practical guidance for managing the supply chain, with an emphasis on health commodities. It is intended to help programme managers who design, manage, and assess logistics systems for health programs. In addition, policymakers, system stakeholders, and anyone working in logistics will also find it helpful as a system overview and overall approach. Available at http://j.mp/1bGeeMh

New assessment guide and tool for HR capacity development in the public health supply chain. Effective public health supply chains require motivated and skilled staff with competency in various essential logistics functions. In an effort to help public health supply chain managers in developing countries assess and improve the management of their human resources, a new toolkit is available at http://j.mp/13n5mre

In highlighting HIV and AIDS prevention and treatment efforts, The project’s updated CD toolkit, *Resources for Managing the HIV & AIDS and Laboratory Supply Chains*, is now available. The CD contains a selection of tools, reports, and briefs for supply chain and programme managers and advisors involved in designing, implementing, and managing in-country supply chains for HIV and AIDS and laboratory commodities available at http://j.mp/16MeTeo

The Number 2, 2013 issue of the *Supply Chain Management (SCM) Newsletter* is available at http://j.mp/1cRZlnN

**Reference:** USAID Deliver Project at http://deliver.jsi.com/
Consultation Documents

The International Pharmacopoeia

Aciclovirum
Aciclovir

This is a draft proposal for The International Pharmacopoeia (June 2013). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax: +41 22 791 4730 or e-mail to schmidt@who.int. Working documents are available for comment on-line at http://www.who.int/medicines.

Molecular formula. \( \text{C}_8\text{H}_{11}\text{N}_5\text{O}_3 \)

Relative molecular mass. 225.20

Chemical name. 2-Amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6H-purin-6-one. CAS Reg. No. 59277-89-3.

Description. White or almost white, crystalline powder.

Solubility. Slightly soluble in water; freely soluble in dimethyl sulfoxide; very slightly soluble in ethanol (96%). It dissolves in dilute solutions of mineral acids and alkali hydroxides.

Category. Antiviral (purine nucleoside analogue).

Storage. Preserve in well-closed containers. Protect from light and moisture.

Additional information. Aciclovir may exhibit polymorphism.

Requirements

Definition. Aciclovir contains not less than 98.5% and not more than 101.0% of \( \text{C}_8\text{H}_{11}\text{N}_5\text{O}_3 \) calculated with reference to the dried substance.

Identity tests

Either test A alone, or test B and D or test C and D may be applied.
A. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from aciclovir RS or with the reference spectrum of aciclovir.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions given under Guanine and related substances test A1. The principal spot in the chromatogram obtained with solution (B) corresponds in position, appearance and intensity to the spot due to aciclovir in the chromatogram obtained with solution (C).

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Guanine and related substances test B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the aciclovir peak in the chromatogram obtained with solution (4).

D. Dissolve about 10 mg of the test substance in 5.0 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 100.0 ml with water R. Dilute 5.0 ml of this solution to 50.0 ml with water R. The absorption spectrum (1.6) of the resulting solution, when observed between 230 nm and 350 nm, exhibits a maximum at about 255 nm and the absorption at 255 nm is about 0.5.

**Clarity and colour of solution.** A solution, containing 0.25 g of the test substance in 25 ml of sodium hydroxide (0.1 mol/l) TS, is clear and not more intensely coloured than standard colour solution Yw1 when compared as described under 1.11 Colour of liquids.

**Sulfated ash (2.3).** Not more than 1.0 mg/g.

**Loss on drying.** Dry to constant mass at 105 °C; it loses not more than 60 mg/g.

**Guanine and related substances**

Either test A or test B may be applied.

A. Carry out test A.1 and A.2.

A.1 Guanine. Carry out the test as described under 1.14.1 Thin-layer chromatography, using cellulose R1 as the coating substance (Merck cellulose F plate has been found suitable) and a mixture of 10 volumes of propan-1-ol, 30 volumes of ammonia (260 g/l) TS and 60 volumes of ammonium sulfate (50 g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of the following four, freshly prepared solutions in sodium hydroxide (0.1 mol/l) TS. For solution (A) use 5 mg of the test substance per ml. For solution (B) dilute 1 volume of solution (A) to 10 volumes. For solution (C) use a solution of 0.5 mg of aciclovir RS and 0.5 mg of guanine R per ml. For solution (D) use 35 µg of guanine R per ml. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air and examine the chromatogram under ultraviolet light (254 nm). In the chromatogram obtained with solution (C) guanine is eluted with a Rf value of 0.5 and aciclovir with a Rf value of 0.7. The test is not valid unless this chromatogram shows two clearly separated spots. Any secondary spot corresponding to guanine in the chromatogram obtained with solution (A) is not more intense than the principal spot in the chromatogram obtained with solution (D) (0.7%).
A.2 Related substances. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R4 as the coating substance and a mixture of 2 volumes of ammonia (260 g/l) TS, 20 volumes of methanol R and 80 volumes of dichloromethane R as the mobile phase. Apply separately to the plate 2 µl of each of the following three, freshly prepared solutions in dimethyl sulfoxide R. For solution (A) use 25 mg of the test substance per ml. For solution (B) dilute 1 volume of solution (A) to 200 volumes. For solution (C) use a mixture of 0.5 mg of aciclovir RS and 0.5 mg of aciclovir impurity A RS per ml. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air and examine the chromatogram under ultraviolet light (254 nm). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots. Any spot with an Rf value greater than that of the principal spot in the chromatogram obtained with solution (A) is not more intense than the principal spot in the chromatogram obtained with solution (B) (0.5%).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl group (5 µm). (Dionex C18 column and Shiseido MG C18 column have been found suitable.)

Use the following conditions for gradient elution:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (%v/v)</th>
<th>Mobile phase B (%v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
<tr>
<td>5–27</td>
<td>100 to 80</td>
<td>0 to 20</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>27–40</td>
<td>80</td>
<td>20</td>
<td>Isocratic</td>
</tr>
<tr>
<td>40–42</td>
<td>80 to 100</td>
<td>20 to 0</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>42–52</td>
<td>100</td>
<td>0</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Maintain the column at 30 °C.

Prepare the following solutions. For solution (1) dissolve 25 mg of the test substance in 5.0 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 25.0 ml with water R. For solution (2) dilute 1.0 ml of solution (1) to 100.0 ml with water R. Dilute 1.0 ml of this solution to 10.0 ml with water R. For solution (3) dissolve 10 mg of guanine R in 10 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 100.0 ml with water. Dilute 5.0 ml of this solution to 50.0 ml with water R. For solution (4) dissolve 5 mg of aciclovir RS, 5 mg of guanine R and 10 mg of aciclovir impurity C RS in 10 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 100 ml with water R.

Inject separately 20 µl each of solutions (1), (2), (3) and (4). Record the chromatograms for about 45 minutes.
In the chromatogram obtained with solution (4) the peak of aciclovir impurity C is eluted with a relative retention time of 0.94 with reference to the peak of aciclovir. The test is not valid unless the resolution factor between the peak due to aciclovir impurity C and the peak due to aciclovir is at least 1.5.

In the chromatogram obtained with solution (1):

- The area of any peak corresponding to guanine is not greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (3) (0.7 %).
- The area of any other peak, other than the principal peak and the peak due to guanine, is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).
- The sum of all other areas, other than the principal peak and the peak due to guanine, is not greater than 8 times the area of the principal peak obtained with solution (2) (0.8%).

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

Dissolve about 0.150 g, accurately weighed, in 60 ml of anhydrous acetic acid R. Titrate with perchloric acid (0.1 mol/l) VS, determining the end-point potentiometrically as described under 2.6 Non-aqueous titrations. Carry out a blank titration. Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 22.52 mg of acyclovir (C\textsubscript{18}H\textsubscript{11}N\textsubscript{5}O\textsubscript{3}).

Impurities

A. 2-[(2-amino-6-oxo-1,6-dihydro-9\textsubscript{H}-purin-9-yl)methoxy]ethyl acetate,

B. 2-amino-1,7-dihydro-6\textsubscript{H}-purin-6-one (guanine),
C. 2-amino-7-[(2-hydroxyethoxy)methyl]-1,7-dihydro-6H-purin-6-one,

F. N-[9-[(2-hydroxyethoxy)methyl]-6-oxo-6,9-dihydro-1H-purin-2-yl]acetamide,

G. 2-[[2-(acetylamino)-6-oxo-1,6-dihydro-9H-purin-9-yl]methoxy]ethyl acetate,

I. 2-amino-7-[[2-[2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl]methoxy]ethoxy]methyl]-1,7-dihydro-6H-purin-6-one,

J. 9,9′-[ethylenebis(oxyethylene)]bis(2-amino-1,9-dihydro-6H-purin-6-one),
K. 2,2′-[methyleneдиimino]bis[9-[(2-hydroxyethoxy)methyl]1,9-dihydro-6$H$-purin-6-one],

L. $N$-(9-acetyl-6-oxo-6,9-dihydro-1$H$-purin-2-yl)acetamide ($N2,9$-diacylguanine),

M. 2-[[2-(acetylamino)-6-oxo-1,6-dihydro-7$H$-purin-7-yl]methoxy]ethyl acetate,

N. unknown structure

O. unknown structure

P. 2-amino-9-(2-hydroxyethyl)1,9-dihydro-6$H$-purin-6-one.
New reference substances

Aciclovir RS
Aciclovir impurity A RS
Aciclovir impurity C RS

New reagents

Guanine R
C$_5$H$_5$N$_5$O, 2-Amino-1,7-dihydro-6H-purin-6-one.

Amorphous white or almost white powder, practically insoluble in water, slightly soluble in ethanol (96 per cent). It dissolves in ammonia and in dilute solutions of alkali hydroxides.

Test Solutions to be added

Ammonium sulfate (50 g/l) TS
Transfer 50 g ammonium sulfate R in a 1000 ml volumetric flask and make up to volume with water R.

Phosphate buffer, pH 2.5, TS
Dissolve 3.48 g of dipotassium hydrogen phosphate R in 1000 ml of water R and adjust to pH 2.5 with phosphoric acid R.

Phosphate buffer, pH 3.1, TS
Dissolve 3.48 g of dipotassium hydrogen phosphate R in 1000 ml of water R and adjust to pH 3.1 with phosphoric acid R.

Acicloviri ad injectionem

Aciclovir for injection

This is a draft proposal for The International Pharmacopoeia (June 2013). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax: +41 22 791 4730 or e-mail to schmidt@who.int. Working documents are available for comment on-line at http://www.who.int/medicines.

Description. A white powder or loose lumps; odourless or almost odourless.

Category. Antiviral (Purine nucleoside analogue).

Storage. Preserve in well-closed containers. Protect from light and moisture.

Labelling. The label should state that the active ingredient is Aciclovir.

**Requirements**

The powder for injections and the reconstituted solution for injection comply with the monograph on Parenteral preparations.

**Definition.** Aciclovir for injection is a sterile powder prepared from Aciclovir with the aid of a suitable alkali. The container of Aciclovir for injection contains not less than 95.0% and not more than 105.0% of the labeled amount of aciclovir (C₈H₁₁N₅O₃).

**Identity tests**

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

A. To a quantity of the test substance, containing the equivalent of about 100 mg of aciclovir, add 10 ml water R, adjust to pH 4–7 with hydrochloric acid (0.1 mol/l) TS and allow to stand for 30 minutes. Filter, use 20 ml water R to wash the precipitate and dry it at 105 °C for 3 hours. Carry out the test with the precipitate as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from aciclovir RS or with the reference spectrum of aciclovir. If the spectra thus obtained are not concordant repeat the test by separately adding 10 ml of water R to the test substance and aciclovir RS and preceding as described. The infrared absorption spectrum is concordant with the spectrum obtained from aciclovir RS.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions given under Guanine and related substances test A1. The principal spot in the chromatogram obtained with solution (B) corresponds in position, appearance and intensity to the spot due to aciclovir in the chromatogram obtained with solution (C).

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay test A. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the aciclovir peak in the chromatogram obtained with solution (2).

D. The absorption spectrum (1.6) of the solution, prepared as described under Assay test B, when observed between 230 nm and 350 nm, exhibits a maximum at 255 nm.

**Clarity and colour of solution.** A solution, containing the equivalent to 0.10 g of aciclovir in 10 ml of water R, is clear and not more intensely coloured than standard colour solution Yw1 when compared as described under 1.11 Colour of liquids.

**Water.** Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A. Use 0.5 g of the test substance. The water content is not more than 55 mg/g.

**pH value.** pH of a solution containing the equivalent to 25 mg of aciclovir per ml of water R, 10.7–11.7.

**Guanine and related substances**

Either test A or test B may be applied.

A. Carry out test A.1 and A.2.
A.1 Guanine. Carry out the test as described under 1.14.1 Thin-layer chromatography, using cellulose R1 as the coating substance (Merck cellulose F plate has been found suitable.) and a mixture of 10 volumes of propan-1-ol, 30 volumes of ammonia (260 g/l) TS and 60 volumes of ammonium sulfate (50 g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of the following four, freshly prepared solutions in sodium hydroxide (0.1 mol/l) TS. For solution (A) dissolve a quantity of the powder to obtain a solution containing 5 mg of Aciclovir per ml. For solution (B) dilute 1 volume of solution (A) to 10 volumes. For solution (C) use a solution of 0.5 mg of aciclovir RS and 0.5 mg of guanine R per ml. For solution (D) use 35 µg of guanine R per ml. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air and examine the chromatogram under ultraviolet light (254 nm). In the chromatogram obtained with solution (C) guanine is eluted with a Rf value of 0.5 and aciclovir with a Rf value of 0.7. The test is not valid unless this chromatogram shows two clearly separated spots. Any secondary spot corresponding to guanine in the chromatogram obtained with solution (A) is not more intense than the principal spot in the chromatogram obtained with solution (D) (0.7%).

A.2 Related substances. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R4 as the coating substance and a mixture of 2 volumes of ammonia (260 g/l) TS, 20 volumes of methanol R and 80 volumes of dichloromethane R as a mobile phase. Apply separately to the plate 2 µl of each of the following three, freshly prepared solutions in dimethyl sulfoxide R. For solution (A) dissolve a quantity of the powder for injection to obtain a solution containing 25 mg of aciclovir per ml. For solution (B) dilute 1 volume of solution (A) to 200 volumes. For solution (C) use a mixture of 0.5 mg of aciclovir RS and 0.5 mg of aciclovir impurity A RS per ml. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air and examine the chromatogram under ultraviolet light (254 nm). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots. Any spot with an Rf value greater than that of the principal spot in the chromatogram obtained with solution (A) is not more intense than the principal spot in the chromatogram obtained with solution (B) (0.5%).

B. 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 silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl group (5 µm). (DionexC18 and Shiseido MG C18 column have been found suitable.)

Use the following conditions for gradient elution:

<table>
<thead>
<tr>
<th>Mobile phase A</th>
<th>Mobile phase B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 volume of acetonitrile R and 99 volumes of phosphate buffer, pH 3.1, TS.</td>
<td>50 volumes of acetonitrile R and 50 volumes of phosphate buffer, pH 2.5, TS.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (%v/v)</th>
<th>Mobile phase B (%v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
<tr>
<td>5–27</td>
<td>100 to 80</td>
<td>0 to 20</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>27–40</td>
<td>80</td>
<td>20</td>
<td>Isocratic</td>
</tr>
<tr>
<td>40–42</td>
<td>80 to 100</td>
<td>20 to 0</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>42–52</td>
<td>100</td>
<td>0</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>
Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Maintain the column at 30 °C.

Prepare the following solutions. For solution (1) dissolve a quantity of the powder for injection, equivalent to 25 mg of aciclovir in 5.0 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 25.0 ml with water R. For solution (2) dilute 1.0 ml of solution (1) to 100.0 ml with water. For solution (3) dissolve 10 mg of guanine R in 10 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 100.0 ml with water R. For solution (4) dissolve 5 mg of aciclovir RS, 5 mg of guanine R and 10 mg of aciclovir impurity C RS in 10 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 100 ml with water R.

Inject separately 20 μl each of solutions (1), (2), (3) and (4). Record the chromatograms for about 45 minutes.

In the chromatogram obtained with solution (4) the peak of aciclovir impurity C is eluted with a relative retention time of 0.94 with reference to the peak of aciclovir. The test is not valid unless the resolution factor between the peak due to aciclovir impurity C and the peak due to aciclovir is at least 1.5.

In the chromatogram obtained with solution (1):

- The area of any peak corresponding to guanine is not greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (3) (0.7 %).
- The area of any other peak, other than the principal peak and the peak due to guanine, is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).
- The sum of all other areas, other than the principal peak and the peak due to guanine, is not greater than 8 times the area of the principal peak obtained with solution (2) (0.8%).

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 test A or test B may be applied.

A. 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 silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl group (5 μm). (Dionex C18 column and Shiseido MG C18 column have been found suitable.)

As the mobile phase, use a mixture of 90 volumes of Mobile phase A, as described under Guanine and related substances test B, and 10 volumes of acetonitrile R.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Maintain the column at 30 °C.
Prepare the following solutions. For solution (1) dissolve a quantity of the powder for injection, equivalent to about 20 mg of aciclovir, accurately weighed, in 10 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 100 ml with water. Dilute 5.0 ml of this solution to 50 ml with water. For solution (2) dissolve 20 mg of aciclovir RS in 10 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 100 ml with water. Dilute 5.0 ml of this solution to 50 ml with water.

Inject separately 20 µl each of solution (1) and (2). Record the chromatograms for about 20 min.

Measure the areas of the peak responses obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of aciclovir (\((\text{C}_8\text{H}_{11}\text{N}_5\text{O}_3)\)) per sealed container, using the declared content of (\((\text{C}_8\text{H}_{11}\text{N}_5\text{O}_3)\)) in aciclovir RS.

B. Mix the contents of 5 containers. Transfer a quantity of the powder for injection, equivalent to 150 mg of Aciclovir, accurately weighed, to a 100 ml volumetric flask and dilute to volume with hydrochloric acid (0.1 mol/l) TS, mix and filter. Dilute 1.0 ml of the resulting solution to 100.0 ml with hydrochloric acid (0.1 mol/l) TS. Measure the absorbance of this solution in a 1 cm layer at 255 nm, using hydrochloric acid (0.1 mol/l) TS as the blank. Calculate the percentage content of aciclovir (\((\text{C}_8\text{H}_{11}\text{N}_5\text{O}_3)\)) per sealed container, using an absorptivity value of 56.0. i.e., \(A = \frac{10.0}{\text{cm}}\).

**Bacterial endotoxins.** Carry out the test as described under 3.4 Test for bacterial endotoxins. Contains not more than 0.17 IU of endotoxin per mg of aciclovir.

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**Acicloviri compressi**

**Aciclovir tablets**

This is a draft proposal for *The International Pharmacopoeia* (June 2013). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax: +41 22 791 4730 or e-mail to schmidt@who.int. Working documents are available for comment on-line at http://www.who.int/medicines.

**Category.** Antiviral (purine nucleoside analogue).

**Storage.** Preserve in well-closed containers. Protect from light and moisture.

**Additional information.** Strength in the current WHO Model List of Essential Medicines: 200 mg. Strengths in the current WHO Model List of Essential Medicines for Children: 200 mg.

**Requirements**

Complies with the monograph on Tablets.

**Definition.** Aciclovir tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of aciclovir (\((\text{C}_8\text{H}_{11}\text{N}_5\text{O}_3)\)).
Identity tests

Either test A and C or test B and C may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions given under Guanine and related test A1. The principal spot in the chromatogram obtained with solution (B) corresponds in position, appearance and intensity to the spot due to aciclovir in the chromatogram obtained with solution (C).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay test A. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the aciclovir peak in the chromatogram obtained with the solution (2).

C. The absorption spectrum (1.6) of the solution, prepared as described under Assay test B, when observed between 230 nm and 350 nm, exhibits a maximum at 255 nm.

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 ml of Hydrochloric acid (~4 g/l) TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of 10 ml of the medium through an in-line filter. Measure the absorbance (1.6) of the filtered sample, suitably diluted if necessary, at a wavelength of 255 nm. At the same time measure the absorbance of a suitable solution of aciclovir RS in hydrochloric acid (~4 g/l) TS, using the same buffer as the blank.

For each of the six tablets tested calculate the total amount of aciclovir (C₈H₁₁N₅O₃) in the medium from the absorbances obtained, using the declared content of C₈H₁₁N₅O₃ in aciclovir RS. Use the requirements as described under 5.5 Dissolution test for solid oral dosage forms, Acceptance criteria to evaluate the results: the amount in solution is not less than 75% (Q) of the amount declared on the label.

Guanine

Either test A or test B may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography, using cellulose R1 as the coating substance (Merck cellulose F plate has been found suitable) and a mixture of 10 volumes of propan-1-ol, 30 volumes of ammonia (260 g/l) and 60 volumes of ammonium sulfate (50 g/l). Apply separately to the plate 10 µL of each of the following four, freshly prepared solutions in sodium hydroxide (0.1 mol/l) TS. For solution (A) shake a quantity of the powdered tablets, containing about 25 mg of aciclovir, with 5 ml of sodium hydroxide (0.1 mol/l) TS, filter and use the filtrate. For solution (B) dilute 1 volume of (A) to 10 volumes. For solution (C) use a solution of 0.5 mg of aciclovir RS and 0.5 mg of guanine RS per ml. For solution (D) use 50 µg of guanine R per ml. After removing of the plate from the chromatographic chamber allow it to dry exhaustively in air and examine the chromatogram under ultraviolet light (254 nm). In the chromatogram obtained with solution (C) guanine is eluted with a Rf value of 0.5 and aciclovir with a Rf value of 0.7. The test is not valid unless this chromatogram shows two clearly separated spots. Any secondary spot corresponding to guanine in the chromatogram obtained with solution (A) is not more intense than the principal spot in the chromatogram obtained with solution (D) (1.0%).

B. Carry out the test as described under 1.14.4 High performance liquid chromatography, using the conditions given under Assay test A.
Prepare the following solutions. For solution (1) shake a quantity of the powdered tablets, containing 25 mg of aciclovir, with 5.0 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 25.0 ml with water, filter and use the filtrate. For solution (2) dissolve 10 mg of guanine R in 10 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 100.0 ml with water R. Then dilute 5.0 ml of this solution to 50.0 ml with water. For solution (3) dissolve 5 mg of aciclovir RS, 5 mg of guanine R in 10 ml of sodium hydroxide (0.1 mol/l) TS and dilute to 100 ml with water R.

Inject 20 µl of solution (3). The test is not valid unless the resolution between the peak due to aciclovir and the peak due to guanine is at least 3.0.

Inject separately 20 µl each of solutions (1) and (2). In the chromatogram obtained with solution (1) the area of any peak corresponding to guanine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Assay

Either test A or test B may be applied.

A. 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 silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl group (5 µm). (Dionex C18 column and Shiseido MG C18 column have been found suitable.)

As the mobile phase, use a mixture of 90 volumes of phosphate buffer, pH 3.1, TS and 10 volumes of acetonitrile R.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Maintain the column at 30 °C.

Prepare the following solutions. For solution (1) shake a quantity of the powdered tablets, equivalent to about 20 mg of aciclovir, accurately weighed, with 10 ml of sodium hydroxide (0.1 mol/l) and dilute to 100 ml with water. Dilute 5.0 ml of this solution to 50 ml with water. For solution (2) dissolve 20 mg of aciclovir RS in 10 ml of sodium hydroxide (0.1 mol/l) and dilute to 100 ml with water. Dilute 5.0 ml of this solution to 50 ml with water.

Inject separately 20 µl each of the solutions (1) and (2). Record the chromatograms for about 20 min.

Measure the areas of the peak responses obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of aciclovir (C₈H₁₁N₅O₃) in the tablets, using the declared content of C₈H₁₁N₅O₃ in aciclovir RS.

B. Weigh and powder 20 tablets. Transfer a quantity of the powder, equivalent to about 0.1 g of Aciclovir, accurately weighed, to a 100 ml volumetric flask, add 60 ml of sodium hydroxide (0.1 mol/l), sonicate for about 15 minutes, allow to cool to room temperature and make up to volume with the same solvent, shake and filter. Transfer 15.0 ml of the filtrate to a 100 ml volumetric flask, add 50 ml of water and 5.8 ml of hydrochloric acid (70g/l) TS and dilute to volume with water R. Dilute 5.0 ml of the solution to 50.0 ml with hydrochloric acid (0.1 mol/l) TS. Measure the absorbance of
the resulting solution in a 1 cm layer at 255 nm, using hydrochloric acid (0.1 mol/l) TS
as the blank. Calculate the percentage content of aciclovir (C_8H_11N_5O_3) in the tablets,
using an absorptivity value of using an absorptivity value of 56.0, i.e.,  
\[ A_{1\% \text{t}1\text{cm}} = 560 \]

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### Radiopharmaceuticals: general monograph

This is a draft general monograph revision for *The International Pharmacopoeia* (June 2013). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax: +41 22 791 4730 or e-mail to schmidth@who.int. Working documents are available for comment on-line at http://www.who.int/medicines.

This general monograph is intended to be read in conjunction with the individual monographs on radiopharmaceutical preparations. A radiopharmaceutical preparation that is the subject of an individual monograph in *The International Pharmacopoeia* complies with the general requirements stated below and with the general monograph for the relevant dosage form (most commonly that for parenteral preparations) as modified by any of the requirements given below and by any specific instruction included in the individual monograph.

**REQUIREMENTS**

**Definition**

**Radiopharmaceutical preparation or radiopharmaceutical.** A radiopharmaceutical preparation or radiopharmaceutical is a medicinal product in a ready-to-use form suitable for human use that contains a radionuclide. The radionuclide is integral to the medicinal application of the preparation, making it appropriate for one or more diagnostic or therapeutic applications.

For the purpose of this general monograph radiopharmaceuticals also cover:

- **Radionuclide generator.** A system in which a daughter radionuclide (short half-life) is separated by elution or by other means from a parent radionuclide (long half-life) and later used for production of a radiopharmaceutical preparation.

- **Radionuclide precursor.** A “radionuclide precursor” means any radionuclide not being a radiopharmaceutical or generator or radionuclide kit which is produced for the radiolabelling of another substance for administration.

- **Kit for radiopharmaceutical preparation.** In general a vial containing the non-radionuclide components of a radiopharmaceutical preparation, usually in the form of a sterilized, validated product to which the appropriate radionuclide is added or in which the appropriate radionuclide is diluted before medical use. In most cases the kit is a multidose vial and production of the radiopharmaceutical preparation may require additional steps such as boiling, heating, filtration and buffering.

- **Chemical precursor.** Non-radioactive substances in combination with radionuclide.
Manufacture

The manufacturing process for radiopharmaceutical preparations should meet the requirements of good manufacturing practice (GMP).

The manufacturer is responsible for ensuring the quality of his products and especially for examining preparations of short-lived radionuclides for long-lived impurities after a suitable period of decay. In this way, the manufacturer ensures that the manufacturing processes employed are producing materials of appropriate quality. In particular, the radionuclide composition of certain preparations is determined by the chemical and isotopic composition of the target material (see “Target materials”) and pilot preparations are advisable when new batches of target material are employed.

When the size of a batch of a radiopharmaceutical preparation is limited to one or few units (for example, certain therapeutic preparations or very short-lived preparations) release of the product must rely on the process control rather than product quality control tests. Therefore validation and revalidation of manufacture process must be fully implemented as well as the product quality control tests.

Radiation Protection. The relevant premises and equipment must be designed, built and maintained so that they do not bear any negative impact on or represent any hazard to the product, personnel or immediate surroundings. The corresponding supporting materials are provided by various IAEA publications.


Radionuclide production. In general ways of manufacturing radionuclides for use in radiopharmaceutical preparations are:

**Nuclear fission.** Nuclides with high atomic number are fissionable and a common reaction is the fission of uranium-235 by neutrons in a nuclear reactor. For example, iodine-131, molybdenum-99 and xenon-133 can be produced in this way. Radio-nuclides from such a process must be carefully controlled in order to minimize the radionuclidic impurities.

**Charged particle bombardment.** Radionuclides may be produced by bombarding target materials with charged particles in particle accelerators such as cyclotrons. The isotopic composition and purity of the target material will influence the radionuclidic purity of irradiated target.

**Neutron bombardment.** Radionuclides may be produced by bombarding target materials with neutrons in nuclear reactors. The rate of the nuclear reaction
depends on the energy of the incident particle, neutron flux and nuclear cross-section. The isotopic composition and purity of the target material will influence the radionuclidic purity of irradiated target.

**Radionuclide generator systems.** Radionuclides of short half-life may be produced by means of a radionuclide generator system involving separation of the daughter radionuclide from a long-lived parent by chemical or physical separation. Care must be taken to avoid contamination of daughter radionuclide with parent radionuclide and decay products.

**Starting materials (including chemical precursors and excipients).** In the manufacture of radiopharmaceutical preparations, measures shall be taken to ensure that all ingredients are of appropriate quality, including those starting materials, such as chemical precursors for synthesis, that are produced on a small scale and supplied by specialized producers or laboratories for use in the radiopharmaceutical industry. The actual quantity of radioactive material compared with quantities of excipients is normally very small therefore excipients can greatly influence the quality of the radiopharmaceutical preparation.

**Target materials.** The composition and purity of the target material and the nature and energy of the incident particle will determine the relative percentages of the principal radionuclide and other potential radionuclides (radionuclidic impurities) and thus ultimately the radionuclidic purity. Strict control of irradiation parameters such as beam energy, intensity and duration is also essential. For very short lived radionuclides including the ones present in most positron emission tomography (PET) tracers the determination of radiochemical and radionuclidic purity of radiopharmaceutical preparation before patient use is difficult. Therefore before clinical use of these radionuclides, strict operational conditions and extensive validations are essential. Any subsequent change in operational conditions should be revalidated.

Where applicable (e.g., cyclotron irradiation of solid targets) each new batch of target material must be tested and validated in special production runs before its use in routine radionuclide production and manufacture of radiopharmaceutical preparation. This will ensure that under specified conditions, the target yields a radionuclide in the desired quantity and quality.

**Carriers.** A carrier, in the form of inactive material, either isotopic with the radionuclide, or non-isotopic, but chemically similar to the radionuclide, may be added during radionuclide production and radiopharmaceutical preparation. In some situations it may be added to enhance chemical, physical or biological properties of the radiopharmaceutical preparation. The amount of carrier added must be controlled and sufficiently small for it not to cause undesirable physiological effects.

**Carrier-free preparation.** It is a preparation free from stable isotope of the same element as the radionuclide concerned present in the preparation in the stated chemical form or at the position of the radionuclide in the molecule concerned. When appropriate, specific radioactivity must be measured in the radiopharmaceutical preparation.

**No-carrier added preparation.** It is a preparation to which no stable isotopes of the same element as the radionuclide concerned are intentionally added in the stated
chemical form or at the position of the radionuclide in the molecule concerned. When appropriate specific radioactivity must be measured in the radiopharmaceutical preparation.

**Production of radiopharmaceutical preparation.** Radiopharmaceutical preparations may contain the types of excipients permitted by the general monograph for the relevant dosage form.

**Sterilization.** Radiopharmaceutical preparations intended for parenteral administration are sterilized by a suitable method (see 5.8 Methods of sterilization). Whenever possible, steam sterilization is recommended.

All sterilization processes must be validated.

**Addition of antimicrobial preservatives.** Radiopharmaceutical injections are commonly supplied in multidose containers. The nature of the antimicrobial preservative, if present, is stated on the label or, where applicable, that no antimicrobial preservative is present.

Radiopharmaceutical injections for which the shelf-life is greater than one day and that do not contain an antimicrobial preservative should preferably be supplied in single-dose containers. If, however, such a preparation is supplied in a multidose container, requirements of the general monograph for Parenteral Preparations should apply.

Radiopharmaceutical injections for which the shelf-life is greater than one day and that do contain an antimicrobial preservative may be supplied in multidose containers. After aseptic withdrawal of the first dose, the container should be stored at a temperature between 2° and 8° C and the contents used within 7 days unless otherwise specified.

**Radiation protection**


**Identity tests**

Tests for identity of the radionuclide are included in the individual monographs for radiopharmaceutical preparations. The radionuclide is generally identified by its half-life or by the nature and energy of its radiation or by both as stated in the monograph.

**Other tests**

**Half-life measurement.** The half-life is a characteristic of the radionuclide that may be used for its identification. The half-life is calculated by measuring the variation of radioactivity of a sample to be tested as a function of time. Perform the measurements in the linearity range of a calibrated instrument. Measurements should comply with the R 1.1 Detection and measurement of radioactivity. Approximate half-life can be determined over a relatively short period of time to allow release for use of radiopharmaceutical preparations. The calculated approximate half-life is within the range of the values stated in the individual monograph.
Radionuclidic purity
Radionuclidic impurities may arise during the production and decay of a radionuclide. Potential radionuclidic impurities may be mentioned in the monographs and their characteristics are described in the general monograph: Annexes: Table of physical characteristics. In most cases, to establish the radionuclidic purity of a radiopharmaceutical preparation, the identity of every radionuclide present and its radioactivity must be known.

Technical details of radionuclide identification and radionuclidic purity determination are described in R1.2 Radiation spectrometry and R1.3 Determination of radionuclidic purity. Because the level of radionuclidic impurities, expressed as a percentage of each impurity, may increase or decrease with time, the measured radioactivity of each impurity must be recalculated to the activity during the period of validity of the preparation.

The individual monographs prescribe the radionuclidic purity required and may set limits for specific radionuclidic impurities (for example, molybdenum-99 in technetium-99m). While these requirements are necessary, they are not in themselves sufficient to ensure that the radionuclidic purity of a preparation is sufficient for its clinical use. The manufacturer must examine the product in detail and especially must examine preparations of radionuclides with a short half-life for impurities with a long half-life after a suitable period of decay. In this way, information on the suitability of the manufacturing processes and the adequacy of the testing procedures is obtained. In cases where two or more positron-emitting radionuclides need to be identified and/or differentiated, for example the presence of 18F-impurities in 13N-preparations, half-life determinations need to be carried out in addition to gamma-ray spectrometry.

Radiochemical purity
A radioactive preparation may contain the radionuclide in different chemical forms other than the intended one. Therefore it is necessary to separate the different substances containing the radionuclide and determine the percentage of radioactivity due to the radionuclide concerned associated with the stated chemical form and the contribution to the total radioactivity due to the radionuclide concerned coming from other substances. For this purpose instruments for the detection and measurement of radioactivity are used in combination with a physic-chemical separation technique. Radiochemical purity is assessed by a variety of analytical techniques such as 1.14.4 High-performance liquid chromatography, 1.14.2 Paper Chromatography, 1.14.1 Thin-layer Chromatography and 1.15 Electrophoresis combined with suitable radioactivity measurement described in R1.1 Detection and measurement of radioactivity.

In all cases the radioactivity of each analyte is measured after the separation has been achieved using the stated method.

The radiochemical purity section of an individual monograph may include limits for specified radiochemical impurities, including isomers.

In some cases, it is necessary to determine the physiological distribution of the radiopharmaceutical in a suitable test animal.

Specific radioactivity. Specific radioactivity is defined as radioactivity of a radionuclide per unit mass of the element or of the chemical form concerned. Specific radioactivity is usually calculated taking into account the radioactivity concentration
and the concentration of the chemical substance being studied. Specific radioactivity changes with time. The statement of the specific radioactivity therefore includes reference to a date and, if necessary, time.

Specific radioactivity must be measured in carrier added preparations. For some non-carrier added radiopharmaceutical preparations (for example, receptor ligands) it is important to state specific radioactivity. Individual monographs might state the range of specific radioactivity.

**Chemical purity**
Chemical purity refers to the proportion of the preparation that is in the specified chemical form regardless of the presence of radioactivity; it may be determined by accepted methods of analysis.

In general, limits should be set for chemical impurities in preparations of radiopharmaceuticals if they are toxic or if they modify the labelling process or alter physiological uptakes that are under study or if they result in undesirable interactions (e.g. aluminium can induce flocculation of Tc-99m sulphur colloid). Special attention is necessary for impurities with a pharmacologically active or pharmacodynamic effect even for very low amounts (for example, receptor ligands). Where appropriate, the stereo-isomeric purity has to be verified. In general, the type of limit for inorganic impurities such as arsenic and heavy metals that are specified in monographs for pharmaceutical substances are also valid for radiopharmaceuticals.

Characterize impurities as much as possible. Generic limits can be set for unidentified impurities. The limits has to be chosen carefully considering amounts and toxicity based upon toxicities of starting materials, precursors, possible degradation products and the final product.

**pH**
When required, measure the pH of non-radioactive solutions as described under 1.13 Determination of pH. For radioactive solutions the pH may be measured using a pH indicator strip R.

*[Note from Secretariat: Add pH indicator strip R to the section on Reagents using the following:]*

**pH indicator strip.** R.  
Plastic or paper strip containing multiple segments of different dye-impregnated papers allowing visual determination of pH in the prescribed range by comparison with a master chart.]

**Sterility**
A number of monographs for radiopharmaceuticals contain the requirement that the preparation is sterile. Such preparations comply with 3.2 Test for sterility. The special difficulty arises with the radiopharmaceuticals because of the short half-life of the radionuclide, the small size of batches and the radiation hazards. In the case that the monograph states that the preparation can be released for use before completion of the test for sterility, the sterility test must be started as soon as practically possible in relation to the radiation. If not started immediately, samples are stored under conditions that are shown to be appropriate in order to prevent false negative result.
When the size of the batch of a radiopharmaceutical is limited to one or few samples (e.g., therapeutic or very short-lived radiopharmaceutical preparations), sampling the batch may not be possible. In this case, reliance is on process control rather than the final product control.

**Bacterial endotoxins/pyrogens**

Where appropriate, an individual monograph for a radiopharmaceutical preparation requires compliance with 3.4 Test for bacterial endotoxins. Validation of the test is necessary to exclude any interference or artefact due to the nature of the radiopharmaceutical. The pH of some radiopharmaceutical preparations will require to be adjusted to pH 6.5–7.5 to achieve optimal results.

Where it is not possible to eliminate interference with the test for bacterial endotoxins due to the nature of the radiopharmaceutical, compliance with 3.5 Test for pyrogens may be specified.

**Labelling**

Every radiopharmaceutical preparation must comply with the labelling requirements established under GMP.

*Note from Secretariat: Check that the text is consistent with current GMP text needs to be undertaken in final version.*

The label on the primary container should include:

- A statement that the product is radioactive or the international symbol for radioactivity;
- Name of the radiopharmaceutical preparation;
- Where appropriate, that the preparation is for diagnostic or for therapeutic use;
- Route of administration;
- Total radioactivity present at a stated date and, where necessary, time; for solutions, a statement of the radioactivity in a suitable volume (for example, in MBq per ml of the solution) may be given instead;
- Expiry date and, where necessary, time;
- Batch (lot) number assigned by the manufacturer;
- For solutions, the total volume.

The label on the outer package should include:

- Statement that the product is radioactive or the international symbol for radioactivity;
- Name of the radiopharmaceutical preparation;
- Where appropriate, that the preparation is for diagnostic or for therapeutic use;
- Route of administration;
• Total radioactivity present at a stated date and, where necessary, time; for solutions, a statement of the radioactivity in a suitable volume (for example, in MBq per ml of the solution) may be given instead;

• Expiry date and, where necessary, time;

• Batch (lot) number assigned by the manufacturer;

• For solutions, the total volume;

• Any special storage requirements with respect to temperature and light;

• Where applicable, the name and concentration of any added microbial preservatives or, where necessary, that no antimicrobial preservative has been added.

**Note:** The shipment of radioactive substances is subject to special national and international regulations as regards to their packaging and outer labelling. (Regulations for the Safe Transport of Radioactive Materials. Safety Requirements. No.TS-R-1 (IAEA, Vienna, 2009). For further details and the current guidance consult the IAEA web site at http://www-ns.iaea.org/standards/)

**Storage**
Radiopharmaceuticals should be kept in well-closed containers and stored in an area assigned for the purpose. Storage conditions should be such that the maximum radiation dose rate to which persons may be exposed is reduced to an acceptable level.

Care should be taken to comply with national regulations for protection against ionizing radiation.

Radiopharmaceutical preparations that are intended for parenteral use should be kept in a glass vial, ampoule or syringe that is sufficiently transparent to permit the visual inspection of the contents. Glass containers may darken under the effect of radiation.

**Annexes: Terminology**

**Biological half-life**
The biological half-life \(T_{1/2}^b\) of a radiopharmaceutical is the time taken for the concentration of the pharmaceutical to be reduced 50% of its maximum concentration in a given tissue, organ or whole body, not considering radioactive decay.

**Critical organ**
The critical organ is the organ or tissue which is the most vulnerable to radiation damage. This may not be the target tissue or the tissue that receives the highest dose and therefore the dose to the critical organ will determine the maximum safe dose which can be administered.

**Effective half-life**
The effective half-life \(T_{1/2}^e\) is the actual half-life of a radiopharmaceutical in a given tissue, organ or whole body and is determined by a relationship including both the physical half-life and biological half-lives. The effective half-life is important in calculation of the optimal dose of radiopharmaceutical to be administered and in monitoring the amount of radiation exposure. It can be calculated from the formula:

\[
T_{1/2}^e = \frac{T_{1/2}^p \times T_{1/2}^b}{T_{1/2}^p + T_{1/2}^b}
\]
Where $T_{1/2p}$ and $T_{1/2b}$ are the physical and biological half-lives respectively.

**Half-life**

The time in which the radioactivity decreases to one-half its original value.

**Explanatory note.** The rate of radioactive decay is constant and characteristic for each individual radionuclide. The exponential decay curve is described mathematically by the equation:

$$N = N_0 e^{-\lambda t}$$

where $N$ is the number of atoms at elapsed time $t$, $N_0$ is the number of atoms when $t = 0$, and $\lambda$ is the disintegration constant characteristic of each individual radionuclide. The half-life period is related to the disintegration constant by the equation:

$$T_{1/2} = \frac{0.693}{\lambda}$$

Radioactive decay corrections are calculated from the exponential equation, or from decay tables, or are obtained from a decay curve plotted for the particular radionuclide involved (see Figure 1).

**Figure 1. Master decay chart**

![Master decay chart](image-url)
Isotopes
Atoms of the same element with different atomic mass numbers are called isotopes.

Nuclide
Nuclide is defined as species of atom as characterized by the number of protons, the number of neutrons, and the energy state of the nucleus.

Radioactive concentration
The radioactive concentration of a solution refers to the amount radioactivity per unit volume of the solution. As with all statements involving radioactivity, it is necessary to include a reference date and time of standardization. For radionuclides with a half-life of less than one day, a more precise statement of the reference time is required. Units for radioactive concentration are megaBecquerels per millilitre (MBq/ml).

Since the radioactive concentration will change with time due to decrease in the nuclide radioactivity it is always necessary to provide a reference time. For short-lived radionuclides the reference time will be more precise including time of day in addition to date.

Radioactive decay
The property of unstable nuclides during which they undergo a spontaneous transformation within the nucleus. This change results in the emission of energetic particles or electromagnetic energy from the atoms and the production of an altered nucleus.

Explanatory note. The term “disintegration” is widely used as an alternative to the term “transformation”. Transformation is preferred as it includes, without semantic difficulties, those processes in which no particles are emitted from the nucleus.

Radioactivity
Generally the term “radioactivity” is used both to describe the phenomenon of radioactive decay and to express the physical quantity of this phenomenon. The radioactivity of a preparation is the number of nuclear disintegrations or transformations per unit time. In the International System (SI), the term “activity” is used, which corresponds to radioactivity in the context of this general monograph.

It is expressed in becquerel (Bq), which is 1 nuclear transformation per second.

Explanatory note. The term “disintegration” is widely used as an alternative to the term “transformation”. Transformation is preferred as it includes, without semantic difficulties, those processes in which no particles are emitted from the nucleus.

Radiochemical purity
The ratio expressed as a percentage of radioactivity of radionuclide concerned which is present in the radiopharmaceutical preparation in the stated chemical form, to the total radioactivity of that radionuclide present in the radiopharmaceutical preparation. Relevant potential radiochemical impurities are listed with their limits in the individual monographs. (Note: Source of information: European Pharmacopoeia.)

As radiochemical purity may change with time, mainly because of radiolysis or chemical decomposition, the result of the radiochemical purity test should be started at given date and if necessary hour indicating when the test was carried out. The radiochemical purity limit should be valid during the whole shelf-life.
Radionuclidic purity
The radionuclidic purity is the ratio expressed as a percentage of radioactivity of the radionuclide concerned to the total radioactivity of the radiopharmaceutical preparation. The relevant potential radionuclidic impurities are listed with their limits in their individual monographs.

Specific radioactivity
The specific radioactivity of a radionuclide corresponds to the SI term “specific activity” in the context of this monograph and is defined as radioactivity of radionuclide per unit mass of the element or of the chemical form concerned, e.g., Bq/g or Bq/mole.

The term employed in radiochemical work is “specific activity”. As the word “activity” has other connotations in a pharmacopoeia, the term should, where necessary, be modified to “specific radioactivity” to avoid ambiguity.

Units of radioactivity
The activity of a quantity of radioactive material is expressed in terms of the number of spontaneous nuclear transformations taking place in unit time. The SI unit of activity is the becquerel (Bq), a special name for the reciprocal second (s⁻¹). The expression of activity in terms of the becquerel therefore indicates the number of transformations per second.

The historical unit of activity is the curie. The curie (Ci) is equivalent to 3.7 x 10¹⁰ Bq. The conversion factors between becquerel and curie and its submultiples are given in Table 1.

Table 1. Units of radioactivity commonly encountered with radiopharmaceuticals and the conversions between SI units and historical units

<table>
<thead>
<tr>
<th>Number of atoms transforming per second</th>
<th>SI unit: becquerel (Bq)</th>
<th>historical unit: curie (Ci)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 Bq</td>
<td>27 picocurie (pCi)</td>
</tr>
<tr>
<td>1000</td>
<td>1 kilobecquerel (kBq)</td>
<td>27 nanocurie (nCi)</td>
</tr>
<tr>
<td>1 x 10⁶</td>
<td>1 megabecquerel (MBq)</td>
<td>27 microcurie (μCi)</td>
</tr>
<tr>
<td>1 x 10⁹</td>
<td>1 gigabecquerel (GBq)</td>
<td>27 millicurie (mCi)</td>
</tr>
<tr>
<td>37</td>
<td>37 Bq</td>
<td>1 (nCi)</td>
</tr>
<tr>
<td>37,000</td>
<td>37 kBq</td>
<td>1 (μCi)</td>
</tr>
<tr>
<td>3.7 x 10⁷</td>
<td>37 MBq</td>
<td>1 (mCi)</td>
</tr>
<tr>
<td>3.7 x 10¹⁰</td>
<td>37 GBq</td>
<td>1 Ci</td>
</tr>
</tbody>
</table>

Annex: Table of physical characteristics

Physical characteristics of clinically relevant radionuclides
Information on the physical characteristics of key radionuclide used in nuclear medicine is provided in Table 2.

Note from Secretariat: Table 2 will be updated by IAEA.
Radiopharmaceuticals

Safety considerations

This is a draft proposed text for the Supplementary Information section of *The International Pharmacopoeia* (June 2013). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax: +41 22 791 4730 or e-mail to schmidth@who.int. Working documents are available for comment on-line at http://www.who.int/medicines.

Safety considerations

Radiopharmaceuticals are radioactive and can pose a risk to the personnel involved in handling them during inter alia manufacture, storage, transport, compounding, testing, dispensing and administration, to the patients to whom they are administered and to the environment.

All personnel involved in any part of the above operations are required to have appropriate specific additional training. All personnel with access to the areas where these operations are carried out, for example, maintenance and support staff such as cleaners should receive specific instruction and appropriate supervision whilst in the operational areas. Risk to patients should be minimized. It is essential to ensure that reproducible and clinically reliable results will be obtained. All operations should be carried out or supervised by personnel who have received expert training in handling radioactive materials.

Specialized techniques are required to minimize the risks to personnel. All procedures in which radiopharmaceuticals are handled must be designed and carried out in compliance with the ALARA principle, that is to ensure that exposure to radiation is as low as reasonably applicable. Three key components of the ALARA principle are time (reduce time of exposure), distance (the greater the distance, the lower the risk) and shielding (appropriate shielding is essential at all stages of handling).

Airborne radioactive contamination is a risk factor. Protection of staff requires a negative pressure environment which is conflicting with the general GMP requirement to protect the product in a positive pressure environment. These issues should be balanced according to risk-based approach and rationalized.

Radiation shielding. Adequate shielding must be used to protect all personnel from ionizing radiation. Additionally, when testing radiopharmaceuticals instruments must be suitably shielded from background radiation.

References

List of IAEA publications (safety, facility design, etc.)

*Note from the Secretariat:* IAEA will provide a list of publications.
Radiopharmaceuticals

Testing: additional guidance

This is a draft proposed text for the Supplementary Information section of The International Pharmacopoeia (June 2013). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax: +41 22 791 4730 or e-mail to schmidth@who.int. Working documents are available for comment on-line at http://www.who.int/medicines.

Note from the Secretariat: It is suggested that the section on “end-user testing/rapid quality control tests” be replaced with the text below.

End-user testing

An end-user test is meant to be the simplified quality control test provided by the respective kit manufacturer in the package leaflet.

The end-user test may be used provided that it can be demonstrated that the preparation is fully traceable to a batch certified to comply with all the other requirements of the related monograph.

End-user testing is an important step in the quality management of radiopharmaceutical preparation and for the safety of patients, especially for those radiopharmaceutical preparations that are dispensed or compounded in the end-user facility (for example, nuclear medicine clinics). Application of the test is specified in the relevant monograph may not be possible at this stage either because of the short half-life of the radioisotope or due to other analytical limitations. The use of alternative, simple tests that adequately identify this radiopharmaceutical preparation is therefore advisable.


Radiopharmaceuticals

Methods of analysis: R3, biological methods

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Note from the Secretariat: In principle, the Secretariat will aim to avoid conclusion of this test in order to avoid tests on animals. The following text is nevertheless proposed to replace the previous version as a general method of analysis.
R3.1 Biodistribution
A physiological distribution test is prescribed for certain radiopharmaceutical preparations. Specific requirements are set out in individual monographs. The distribution pattern of radioactivity observed in specified organs, tissues or other body compartments of an appropriate animal species (usually small animals such as rats or mice) can be a reliable indication of the expected distribution in humans and thus of the suitability of the intended purpose. The individual monograph prescribes the details concerning the performance of the test and the physiological distribution requirements, which must be met for the radiopharmaceutical preparation. A physiological distribution conforming to the requirements will assure appropriate distribution of the radioactive compounds to the intended biological target in humans and limits its distribution to non-target areas. Determination of the biodistribution pattern is usually done in the development phase of a kit, radiopharmaceutical or revalidation of known compound.

Selection of animals
Usually healthy animals are used, except for certain special circumstances such as cancer models, which are drawn from a uniform stock that have not previously been treated with any material which will interfere with the test. If relevant, the species, sex, strain and weight and/or age of the animals are specified in the monograph. Unless otherwise stated, mice weigh not less than 20 g and not more than 30 g; rats weigh not less than 150 g and not more than 250 g; and guinea pigs (especially for cardiac radiopharmaceuticals) weigh not less than 250 g.

Method
Prepare the test radiopharmaceutical, draw required radioactivity in a small volume (e.g. 0.2 mL) into a 1 mL syringe. Inject the specified radioactivity (x) of the radiopharmaceutical preparation into the tail vein of animals (usually three animals). Weight of the animals is measured in advance. Measure the radioactivity in the syringe before (y) and after the injection (z). Swab the injection site with cotton wool and retain the cotton wool and the residual dose in the syringe after injecting for counting (y) and (z), respectively.

Actual injected dose (a) = x-(y+z).

Immediately after injection, place each animal in a separate cage that is designed to allow collection of excreta and to prevent contamination of the body surface of the animal. After the time period specified in the monograph (uptake time), euthanize the animals. Collect a sample of blood by cardiac puncture and record the weight of the sample. Harvest the required organs, e.g., gall bladder, liver, stomach, intestines, bones and kidneys, and place in separate labelled counting tubes. Remove the tail above the injection site and place in a labelled counting tube. Determine the injected dose by an appropriate method depending on the activity.

Standard solutions of the radiopharmaceuticals are prepared. Draw 0.2 mL of the radiopharmaceutical solution in a syringe and estimate its weight by weighing the empty syringe and the syringe with solution and calculating the difference. Dispense this radiopharmaceutical solution into a clean 100 mL glass beaker and add 20 mL of distilled water. This solution is taken as the standard for estimation of the total activity that is injected into the animals. Corrections for different sample geometries are applied when necessary. Decay correction needs to be applied and times of
measurement are recorded. Measurements are done for three times and averaged. Background counts should be subtracted for each measurement.

The activity in the organs, tail and carcass is measured either in an isotope dose calibrator or in a NaI(Tl) crystal scintillation counter which is regularly calibrated.

Biodistribution can be calculated by the following methods.

**Method A**

The percentage activity in the organ is calculated as follows:

If using an isotope dose calibrator, the activity retained in the organs is calculated as:

\[ \text{% injected activity in the organ} = \frac{\text{activity obtained in the organ} \times 100}{\text{total activity injected}} \]

If using a NaI(Tl) scintillation counter, the activity retained in the organs is calculated as:

\[ \text{% injected activity in the organ} = \frac{\text{counts in organ}}{\text{counts in standard} \times (\text{Wi}/\text{Ws})} \times 100 \]

where \( Wi \) is the weight of injection and \( Ws \) is the weight of the standard.

The percentage of radioactivity in blood is determined according to the formula:

\[ \left[ 100 x \left( \frac{C}{Ws} \right) \times 0.07 \times \left( \frac{Wr}{a} \right) \right] \]

where \( C = \) Radioactivity in specimen of blood;
\( Ws = \) weight in grams of blood specimen;
\( Wr = \) weight in grams of animal. (Normally, blood is approx. 7% of total body weight.)

**Method B**

\( (ID/g) \) injected dose per gram of tissue

\[ \% \ ID/g = C_t \times \frac{V_t}{W_t} \frac{1}{D_{inj}} \times 100 \left( \% / g \right) \]

Where \( C_t \) = tissue concentration = activity / volume
\( V_t \) = tissue volume
\( W_t \) = tissue weight
\( D_{inj} \) = dose injected

**Specification**

The preparation meets the requirements of the test if the distribution of radioactivity in at least two of the three animals complies with the criteria specified in the monograph. Disregard the results from any animal showing evidence of extravasation of the injection (observed at the time of injection or revealed by subsequent assay of tissue radioactivity).

Biodistribution studies by organ counting can be supplemented by the gamma camera imaging.
In the development of new radiopharmaceuticals, repeat studies should be done for different time points of organ harvesting (e.g., 1-hour, 3-hour, 6-hour or 24 hour post injection) with a similar number of animals for same cohort group.

Radiopharmaceuticals: specific monograph

**Natriiodidi (\(^{131}\text{I}\)) solutio**  
*Sodiumiodide (\(^{131}\text{I}\)) solution*

This is a draft revised proposal for *The International Pharmacopoeia* (June 2013). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax: +41 22 791 4730 or e-mail to schmidt@who.int. Working documents are available for comment on-line at http://www.who.int/medicines.

**Monograph.** Radiopharmaceuticals: Specific monographs: Natriiiodidi (\(^{131}\text{I}\)) solutio - Sodium iodide (\(^{131}\text{I}\)) solution

**Latin.** Natrii iodidi (\(^{131}\text{I}\)) solutio.

**English.** Sodium iodide (\(^{131}\text{I}\)) solution.

**Structural formula.** Na⁺ I⁻

**Relative molecular mass.** 153.895.

**Empirical formula.** Na \(^{131}\text{I}\)

**Chemical name.** Sodium (\(^{131}\text{I}\)) iodide

**Other names.** Natrii radioiodidum, IodotopeSodium iodide I 131

**Description.** Sodium iodide (\(^{131}\text{I}\)) solution is a clear colourless solution. Iodine-131 has a half-life of 8.08 days.

**Category.** Diagnostic or therapeutic.

**Storage.** Stored at room temperature. Preserve in single-dose or multiple-dose containers that previously have been treated to prevent adsorption.

**Labelling.** State the date and the time of calibration; the amount of \(^{131}\text{I}\) as iodide expressed as total MBq and the concentration expressed as MBq/ml, the expiration date, the name of any excipient, the name and quantity of any added preservative or stabilizer. The label states a statement of the intended use, whether oral or intravenous; a statement of whether the contents are intended for diagnostic or therapeutic use and the statement “Caution-Radioactive material”. The labelling indicates that in making dosage calculations, correction has to be made for radioactive decay, also indicates that the radioactive half-life of 131I is 8.08 days.
Manufacture
Iodine-131 may be obtained by neutron bombardment of tellurium or by extraction from uranium fission products. No carrier iodide is added.

Sodium iodide (131I) solution may contain sodium thiosulfate, sodium hydrogen carbonate or other suitable reducing agents and may contain a suitable buffer. Sodium iodide (131I) solution may be sterilized by «Heating in an autoclave» (see 5.8 Methods of sterilization).

Additional information. Wherever V is used within the tests of this monograph, V is the maximum recommended dose, in millilitres.

Requirements

Complies with the monograph for “Liquid preparations for oral use”, “Parenteral Preparations” and with that for “Radiopharmaceuticals” as appropriate.

Definition. Sodium iodide solution is an aqueous solution containing of radioactive (131I) processed in the form of sodium iodide, suitable for either oral or intravenous administration. The solution contains not less than 90% and not more than 110% of the declared radioactivity due to iodine-131 stated on the label at the reference date and time. Not less than 99.9% of the total radioactivity is due to iodine-131. Not less than 95% of the total iodine-131 radioactivity is present as iodide. It contains minute amounts of naturally occurring iodine 127. The specific radioactivity is not less than 185 MBq (5 mCi) per microgram of iodine at the reference date and time stated on the label. The iodide content should not more than 20 µg in maximum recommended dose.

Identity tests

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

A. Record the gamma-ray and X-ray spectrum using a suitable instrument with a sample of iodine-131, suitably diluted if needed. The spectrum is concordant with the reference spectrum of a specimen of iodine-131 in that it exhibits a major peak of 364 keV. Standardized iodine-131 solutions are available from laboratories recognized by the relevant national or regional authority.

B. The half-life determined using a suitable detector system is between 184 and 203 hours.

C. Examine the radiochromatogram obtained in the test for radiochemical purity. The principal peak in the chromatogram obtained with the test solution (a) is similar in retention time to the principal peak in the chromatogram obtained with the reference solution (a).

pH value. Carry out the test as described under 1.13 Determination of pH or R1.5 under the monograph for “Radiopharmaceuticals”. pH between 7.5 and 9.0 of the solutions intended for parenteral administration and between 7.5 and 10.0 of the solutions intended for oral administration.

Sterility. The solution complies with 3.2.1 Test for sterility of non-injectable preparations, modified as described in the monograph for “Radiopharmaceuticals”.

The International Pharmacopoeia
If intended for intravenous administration it complies with 3.2 Test for sterility for injectable preparation, modified as described in the monograph for “Radiopharmaceuticals”. Test for sterility will be initiated on the day of manufacture. The solution may be released for use before completion of the test.

**Bacterial endotoxins**

Carry out the test as described under 3.4 Test for bacterial endotoxins, for solution intended for intravenous use modified as described in the monograph for “Radiopharmaceuticals”. The injection contains not more than 175/V (I.U of endotoxins per millilitre).

**Radionuclidic purity.** Record the gamma-ray and X-ray spectrum using a suitable instrument and measure the half-life using a suitable method. Determine the relative amounts of iodine-131, iodine-133, iodine-135 and other radionuclidic impurities that may be present. Iodine-133 has a half-life of 20.8 hours and exhibits major peaks of 530 keV and 875 keV. Iodine-135 has a half-life of 6.55 hours and exhibits major peaks of 527 keV, 1132 keV and 1260 keV. Not less than 99.9% of the total radioactivity is due to iodine-131.

**Chemical purity**

**Iodide.** Carry out the test as described under 1.14.4 High-performance liquid chromatography Prepare the test solution (a) which is the preparation to be examined. Prepare the test solution (b) by diluting test solution (a) using 0.05 M sodium hydroxide until the radioactivity is equivalent to about 74 MBq/ml and add an equal volume of a solution containing 1 g/L of potassium iodide R, 2 g/L of potassium iodate R and 10 g/L of sodiumhydrogen carbonate R and mix. The reference solution (a) is prepared by diluting 1 ml of a 26.2 mg/L solution of potassium iodide R to V with water R, (V being the maximum recommended dose in millilitres). Prepare the reference solution (b) by diluting 1 ml of a 24.5 mg/L solution of potassium iodate R to V with water R, (V being the maximum recommended dose in millilitres). Mix equal volumes of this solution and of reference solution (a). Prepare a solution containing 2 mg/ml of each of the components stated on the label, apart from iodide, used as blank solution. Use the column with (l = 0.25 m, Ø = 4.0 mm). The stationary phase is spherical base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 µm), maintain the temperature constant between 20 °C and 30 °C. Use stainless steel tubing.

Dissolve 5.844 g of sodium chloride R in 1000 mL of water R, add 650 µL of octylamine R and adjust to pH 7.0 with phosphoric acid R; add 50 mL of acetonitrile R and mix. Use the mixture as the mobile phase. The flow rate is 1.5 ml/min, the detector is spectrophotometer at 220 nm and radioactivity detector connected in series. Inject 25 µl of test solution (a), the blank solution and reference solutions (a) and (b). The run time is 12 minutes.

The relative retention with reference to iodide is 5 and to iodate is 0.2 to 0.3.

**System suitability**

Regarding the chromatogram due to the blank solution, none of the obtained peaks shows a retention time similar to that of the peak due to iodide. The resolution is a minimum of 2 between the peaks due to iodide and iodate in the chromatogram.
obtained with reference solution (b) recorded with the spectrophotometer. The limit of iodide is detected by studying the chromatogram obtained with the spectrophotometer and comparing the peak due to iodide with the chromatogram due to reference solution (a).

The area of the peak due to iodide is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a).

Radiochemical purity

Either test A, B, or C may be applied:

A. Carry out the test as described under 1.14.2 Paper chromatography and ascending conditions, using paper for chromatography R (25- × 300-mm). Place a measured volume of a solution containing 100 mg of potassium iodide, 200 mg of potassium iodate, and 1 g of sodium bicarbonate and 25 mm from one end of the chromatographic paper. Allow the paper to dry. To the same area of the paper add an equal volume of appropriately diluted solution such that it provides a count rate of about 20,000 counts per minute and allow to dry. Develop the chromatogram over a period of about 4 hours by ascending chromatography, using dilute methanol (7.0 in 10). Allow the paper to dry in air, and determine the radioactivity distribution by scanning with a suitable radiation detector: the radioactivity of the iodide $^{131}$I band is not less than 95% of the total radioactivity, and its $R_F$ value falls within ±5% of the value found for sodium iodide when determined under parallel conditions.

Confirmation of the identity of the iodide band is made by the addition to the suspected iodide band of 6 drops of acidified hydrogen peroxide solution (prepared by adding 6 drops of 1 N hydrochloric acid to 10 mL of hydrogen peroxide solution) followed by the dropwise addition of starch TS; the development of a blue color indicates presence of iodide.

B. Carry out the test 1.14.4 High-performance liquid chromatography as described in the test for iodide with the following modification:

- Inject test solution (b)
- Detect Iodide limit by examination of the radioactivity detector, not less than 95 per cent of the total radioactivity is due to $[^{131}I]$ iodide.

C. Carry out the test as described under 1.15 Electrophoresis, Paper-electrophoresis Prepare paper strips, type Whatman No.3 MM for electrophoresis with dimensions of 65 × 3 cm.

Apply 10–20 μl samples in a distance of 10-13 cm from the end of the stripes. Use borate buffer with a concentration of 9 g/l and pH 9 ± 0.1. Carry out the electrophoresis on a potential of 900 V and time is 50 minutes.

The $R_F$ value for iodide is between 0.7 and 0.9, $R_F$ for iodate is 0.4, periodate from 0 to 0.1. Product can be accepted if the $^{131}$I anion content is higher than 95% even on the expiration date.
**Radioactivity.** Measure the radioactivity as described under R.1.1 Detection and measurement of radioactivity in suitable calibrated counting equipment by comparison with a standardized iodine-131 solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized iodine-131 solutions are available from laboratories recognized by the relevant national or regional authority.

**Impurities**

\[^{131}\text{I}\]\ iodate ion.

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**Radiopharmaceuticals: specific monograph**

**Technetii (\(^{99}\text{Mtc}\)) exametazimi multiplex injectio**

**Technetium (\(^{99}\text{Mtc}\)) exametazime complex injection**

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**Monograph.** Radiopharmaceuticals: Specific monographs: Technetii (\(^{99}\text{mTc}\)) exametazimi multiplex injectio – Technetium (\(^{99}\text{mTc}\)) exametazime complex injection

**Latin.** Technetii (\(^{99}\text{mTc}\)) exametazimi multiplex injection.

**English.** Technetium (\(^{99}\text{mTc}\)) exametazime complex injection.

**Structural formula**

![Structural formula](image)

**Empirical formula.** \(\text{C}_{13}\text{H}_{25}\text{N}_{4}\text{O}_{3}\cdot\text{\(^{99}\text{mTc}\)}\)

**Relative molecular mass.** 384.269
**Chemical name.** Racemic mixture of (3\textit{RS},9\textit{RS})-4,8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime complex with (\textit{99mTc}) technetium.

**Other names.** (\textit{99mTc})-D,L-Hexamethylpropyleneamine oxime complex injection; (\textit{99mTc})-D,L-HMPAO injection.

**Description.** Technetium (\textit{99mTc}) exametazime complex injection is a clear, colourless aqueous solution.

Technetium-\textit{99m} has a half-life of 6.02 hours.

**Category.** Diagnostic.

**Storage.** Technetium (\textit{99mTc}) exametazime complex injection should be kept at a temperature between 2°C to 8°C.

Technetium (\textit{99mTc}) exametazime complex injection should be used within 30 minutes of reconstitution of the unlabelled kit with Technetium-99m, unless the preparation has been stabilized with either cobalt chloride solution or methylene blue solution.

**Labelling.** State the date and the time of calibration; the amount of \textit{99mTc} as labelled exametazime expressed as total MBq and the concentration expressed as MBq/ml; the expiration date; and the statement “Caution — Radioactive material”. The labelling indicates that in making dosage calculations, correction is to be made for radioactive decay, and indicates that the half-life of \textit{99mTc} is 6.02 hours. The label states that upon constitution with Sodium Pertechnetate \textit{99mTc} injection, beyond use time is 30 minutes for the unstabilized injection, and between 4 hours and 6 hours for the stabilized injections.

**Manufacture.** Technetium-99m is a radioactive nuclide formed by the radioactive decay of molybdenum-99. Molybdenum-99 is a radioactive isotope of molybdenum and may be produced by neutron irradiation of natural molybdenum or of molybdenum enriched in molybdenum-98 or it may be produced by uranium fission.

Technetium (\textit{99mTc}) exametazime injection is prepared aseptically from sterile starting materials such as a sterile kit containing a mixture of (\textit{3RS}, \textit{9RS})-4, 8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime and stannous salt with sodium pertechnetate (\textit{99mTc}) injection (fission or non-fission). The injection may have the pH adjusted and may contain stabilizing agents. The injection may also be prepared under aseptic processing combined with sterilization by Filtration (see 5.8 Methods of sterilization).

**Additional information.** Wherever V is used within the tests of this monograph, V is the maximum recommended dose in millilitre.

**Requirements**

Complies with the monograph for “Parenteral Preparations” and with that for “Radiopharmaceuticals”.

**Definition.** Technetium (\textit{99mTc}) exametazime injection is a racemic mixture of (\textit{3RS}, \textit{9RS})-4, 8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime (exametazime).
complexes with sodium pertechnetate ($^{99m}\text{Tc}$) injection (fission or non-fission) in presence of stannous salt. The injection is suitable for intravenous administration and contains sufficient sodium chloride to make the solution isotonic with blood. The content of technetium-99m is not less than 90% and not more than 110% of the content of technetium-99m. Not less than 80% of the total technetium-99m radioactivity is present as lipophilic ($^{99m}\text{Tc}$) exametazime complex.

Identity tests

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

A. Record the gamma-ray spectrum using a suitable instrument with a sample of technetium-99m, suitably diluted if needed. The spectrum is concordant with the reference spectrum of a specimen of technetium-99m in that it exhibits a major peak of 140 keV.

Standardized technetium-99m solutions are available from competent laboratories recognized by the relevant national or regional authority.

B. The half-life determined using a suitable detector system is between 5.72 and 6.32 hours.

C. Examine the chromatograms obtained in the test Impurity A under Radiochemical purity. The principal peak in the chromatogram obtained with the test solution is similar in retention time to the peak due to lipophilic technetium-99m exametazime in the chromatogram obtained with the reference solution.

pH value. Carry out the test as described under 1.13 Determination of pH or R1.5 under the monograph for “Radiopharmaceuticals”. pH of the injection, between 5.0 to 10.0.

Sterility. The injection complies with 3.2 Test for sterility, modified as described in the monograph for “Radiopharmaceuticals”. Test for sterility will be initiated on the day of manufacture. The injection may be released for use before completion of the test.

Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins, modified as described in the monograph for “Radiopharmaceuticals”. The injection contains not more than 175/V I.U of endotoxins per millilitre. The injection may be released for use before completion of the test.

Radionuclidic purity. Record the gamma-ray spectrum using a suitable instrument and measure the half-life using a suitable method. Determine the relative amounts of technetium-99m and radionuclidic impurities that may be present.

Radiochemical purity

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

A. Carry out three separate tests as described under 1.14.2 Paper chromatography and ascending conditions. Use suitable cellulose paper strips and methyl ethyl ketone R (system A) or sodium chloride (9 g/l) TS (system B) as the mobile phases.
Use suitable silica gel impregnated glass fiber paper strips and a mixture of equal volumes of acetonitrile R and water R as the mobile phase (system C). Apply to the paper about 5 μl of the injection to be examined, suitably diluted to give an optimum count rate and develop for a distance of about 15 cm. Allow the paper to dry in air and determine the radioactivity distribution by a suitable method. In system (A), the secondary exametazime complex and reduced hydrolysed technetium-99m have \( R_F \) value of 0, and the lipophilic exametazime complex and the pertechnetate ion have \( R_F \) value of 0.8 to 1.0. In system (B), reduced hydrolysed technetium-99m has \( R_F \) value of 0, and the lipophilic exametazime complex, the secondary exametazime complex and the pertechnetate ion have an \( R_F \) value of 0.8 to 1.0. In system (C), the pertechnetate ion has an \( R_F \) value of 0.8 to 1.0, and the lipophilic exametazime complex, the secondary exametazime complex and reduced hydrolysed technetium-99m have \( R_F \) value of 0. The sum of the percentages of radioactivity corresponding to the pertechnetate ion in system (C) and reduced hydrolysed technetium-99m in system (B) is less than 10%. Not less than 80% of the total technetium-99m radioactivity is present as lipophilic exametazime complex.

B. Impurity C. Carry out the test described under 1.14.1 Thin-layer chromatography for impurity C use TLC silica gel plate R, a glass fiber plate and 9 g/L solution of sodium chloride as a mobile phase. Apply to the plate about 5 μl of the injection to be examined, and develop immediately for a distance over 2/3 of the plate. Allow the plate to dry in air and determine the radioactivity distribution using a suitable detector. Impurity C has \( R_F \) value of 0.8 to 1.0; lipophilic technetium-99m exametazime and impurities A, B, D and E do not migrate. The maximum limit of impurity C is 10 per cent of the total radioactivity.

C. Total of lipophilic technetium-99m exametazime and impurity A. Carry out the test under 1.14.1 Thin-layer chromatography. Use TLC silica gel plate R, a glass fiber plate and methyl ethyl ketone as a mobile phase. Apply to the plate about 5 μl of the injection to be examined, and develop immediately for a distance over 2/3 of the plate. Allow the plate to dry in air and determine the radioactivity distribution using a suitable detector. The lipophilic technetium-99m exametazime, impurities A and C have \( R_F \) value of 0.8 to 1.0; for impurities B, D and E do not migrate. Calculate the percentage of radioactivity due to impurities B, D and E from test C and the percentage of the radioactivity due to impurity C from test B. Calculate the total percentage of lipophilic technetium-99m exametazime and impurity A from the expression: 100-A-B.

Not less than 80% of the total technetium-99m radioactivity is present as lipophilic technetium 99m exametazime and impurity A.

Impurity A. Carry out the test as described under 1.14.4 High-performance liquid chromatography Prepare the reference solution by dissolving the contents of a vial of meso-rich exametazime CRS in 0.5 ml of a 9 g/L solution of sodium chloride and transfer to lead-shielded nitrogen-filled vial. Add 6 μL of a freshly prepared 1 g/L solution of stannous chloride R in 0.05 M hydrochloric acid and 2.5 mL of sodium pertechnetate\(^{99m}\mathrm{Tc}\) injection (fission or non-fission) containing 370-740 MBq. Mix carefully and use within 30 min of preparation. The size of the column used is \( l = 0.25 \text{ m}, \ O = 4.6 \text{ mm} \). The stationary phase is spherical base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 μm) with a pore size of 13 nm.
and a carbon loading of 11 per cent. Mix 33 volumes of acetonitrile R and 67 volumes of 0.1 M phosphate buffer solution R pH 3.0 to use as mobile phase. The flow rate is 1.5 mL/min, the detector is radioactivity detector with loop injector the run time is 20 min. The relative retention with reference to lipophilic technetium-99m exametazime to impurity A is about 1.2.

**System suitability: reference solution**
The produced chromatogram is similar to the chromatogram provided with meso-rich exametazime CRS. The resolution is a minimum of 2 between the peaks due to lipophilic technetium-99m exametazime and to impurity A. Impurity A should not more than 5 per cent of the radioactivity due to lipophilic technetium-99m exametazime and impurity A.

**Chemical purity**

**Tin.** Carry out the test as described under R2.1.4 Tin estimation by UV absorption, using 1.0 ml of a test solution prepared by diluting 1.5 ml of the injection to be examined to 25.0 ml with hydrochloric acid (1 mol/l) VS and mixing thoroughly. Prepare the reference solution by dissolving 0.115 g of stannous chloride R in hydrochloric acid (1 mol/l) VS, diluting to 1000 ml with the same solvent and mixing thoroughly. The absorbance of the test solution is not greater than that of the reference solution; not more than 0.6 µg of Sn per ml.

**Radioactivity.** Measure the radioactivity as described under R.1.1 Detection and measurement of radioactivity in a suitable calibrated counting equipment by comparison with a standardized technetium-99m solution or by measurement in an instrument calibrated with the aid of such a solution (a good approximation may be obtained using an ionization chamber and employing a standardized solution of cobalt-57 provided that correction for the differences in the radiations emitted are made).

Standardized technetium-99m and cobalt-57 solutions are available from laboratories recognized by the relevant national or regional authority.

**Impurities**
A. Meso isomer of lipophilic technetium-99m exametazime,
B. Technetium-99m in colloidal form,
C. [99mTc] pertechnetate ion,
D. Non lipophilic technetium-99m exametazime complex,
E. Meso isomer of non-lipophilic technetium-99m exametazime complex.

**Biodistribution.** Carry out the test as described under R3.1 Biological distribution using a set of three mice. At 5 to 10 minutes post injection not less than 1.5% of the injected radioactivity should be found in the brain and not more than 20% of the injected radioactivity should be found in the intestine. Not more than 15% of the injected radioactivity should be found in the liver.

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**Radiopharmaceuticals: specific monograph**

**thallosi (201Tl) chloridi Injectio**

**thallos (201Tl) chloride injection**

This is a draft revised proposal for *The International Pharmacopoeia* (June 2013). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax: +41 22 791 4730 or e-mail to schmidt@who.int. Working documents are available for comment on-line at http://www.who.int/medicines.

- **Additional or amended text.**

**Monograph.** Radiopharmaceuticals: Specific monographs: Thallosi (201Tl) chloridi injectio – Thallous (201Tl) chloride injection

**Latin.** Thallosi (201Tl) chloridi injectio

**English.** Thallous (201Tl) chloride injection

**Structural formula.** TI+ Cl-

**Empirical formula.** 201TICl

**Relative molecular mass.** 236.423

**Chemical name.** Thallium (201Tl) chloride

**Other names.** Thallous (201Tl) chloride

**Description.** Thallous (201Tl) chloride injection is a clear colourless, aqueous solution. Thallium-201 has a half-life of 73.1 hours.

**Category.** Diagnostic.
Storage. After aseptic withdrawal of the first dose from a multidose container, the container should be stored at a temperature between 2°C to 8°C and the contents used within 7 days.

Labelling. State the date of withdrawal of the first dose for multidose containers. State the time and date of calibration; the amount of $^{201}\text{Tl}$ as labeled thallous chloride expressed as total MBq and concentration as expressed as MBq/ml at the time of calibration; the expiration date; and the statement “Caution—Radioactive Material.” The labeling indicates that in making dosage calculations, correction is to be made for radioactive decay, and also indicates that the radioactive half-life of $^{201}\text{Tl}$ is 73.1 hours.

Manufacture
No-carrier-added thallium-201 radioisotope is produced by proton bombardment of enriched thallium 203 target followed by chemical separation of lead 201 radioactive isotopes. The separated lead isotope decay in optimum 32 hours into thallium 201 by electron capture or positron emission. Separation of thallium-201 may be done using anion-exchange resin chromatography or solvent extraction.

Thallous ($^{201}\text{Tl}$) chloride injection may be sterilized by «Heating in an autoclave» (see 5.8 Methods of Sterilization).

Additional information
Wherever V is used within the tests of this monograph, V is the maximum recommended dose in millilitres.

Requirements
Complies with the monograph for “Parenteral Preparations” and with that for “Radiopharmaceuticals”.

Definition. Thallous ($^{201}\text{Tl}$) chloride injection is a sterile, isotonic, aqueous solution of thallium-201 as thallous chloride, suitable for intravenous administration. It contains sufficient sodium chloride to make the solution isotonic with blood and may contain suitable antimicrobial preservatives such as benzyl alcohol or stabilizing agents.

The injection contains not less than 90% and not more than 110% of the content of thallium-201 at the reference date and time stated on the label. Not less than 97% of the total radioactivity is due to thallium-201. Not more than 2% of the total radioactivity is due to thallium-202. The specific radioactivity is not less than 3.7 GBq (100 mCi) of thallium-201 per milligram of thallium at the reference date and time stated on the label.

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

A. Record the gamma-ray using a suitable instrument with a sample of thallium-201, suitably diluted if needed. The spectrum is concordant with the reference spectrum of a specimen of thallium-201 in that it exhibits major peaks of 135, 166, and 167keV and X-rays of 69 and 83keV.

Standardized thallium-201 solutions are available from laboratories recognized by the relevant national or regional authority.
B. The half-life determined using a suitable detector system is between 70 and 75 hours.

C. Examine the electropherogram obtained in the test for radiochemical purity. The distribution of the radioactivity contributes to the identification of the preparation. pH value. Carry out the test as described under 1.13 Determination of pH or R1.5 under the monograph for “Radiopharmaceuticals”. pH of the injection, 4.0 to 7.0.

Sterility. The injection complies with 3.2 Test for sterility, modified as described in the monograph for “Radiopharmaceuticals”. Test for sterility will be initiated on the day of manufacture. The injection may be released for use before completion of the test. Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins, modified as described in the monograph for “Radiopharmaceuticals”. The injection contains not more than 175/V (I.U. of endotoxins per millilitre). The injection may be released for use before completion of the test.

Radionuclidic purity. Record the gamma-ray and X-ray spectrum using a suitable instrument and measure the half-life using a suitable method. Determine the relative amounts of thallium-200, thallium-201, thallium-202, lead-201, lead 203 and other radionuclidic impurities that may be present. Thallium-202 has a half-life of 12.2 days and exhibits a main peak of 440 keV. Thallium-200 has a half-life of 1.09 days and exhibits main peaks of 368, 579, 828 and 1206 keV. Lead-201 has a half-life of 9.4 hours and exhibits a main peak of 331 keV. Lead-203 has a half-life of 2.17 days and exhibits a main peak of 270 keV. Not less than 97% of the total radioactivity is due to thallium-201. Not more than 2% of the total radioactivity is due to thallium-202.

Standardized solutions of thallium-201 and thallium-202, are available from laboratories recognized by the relevant national or regional authority.

Radiochemical purity. Carry out the test as described under 1.15 Electrophoresis, zone-electrophoresis Prepare a suitable cellulose polyacetate strip as the supporting medium and soak the strip in a solution of disodium edetate R (18.6 g/L) as the electrolyte solution. Soak the strip in the electrolyte solution for 45-60 min. Remove the strip with forceps taking care to handle the outer edges only. Place the strip between 2 absorbent pads and blot to remove excess solution. Apply not less than 5 µl of a mixture of equal volumes of the preparation to be examined and the electrolyte solution to the centre of the blotted strip and mark the point of application. Attach the strip to the support bridge of an electrophoresis chamber containing equal volumes of disodium edetate R in each side of the chamber. Ensure that each end of the strip is in contact with the disodium edetate R. Apply an electric field of 250 volts for at 30 minutes. Allow the strip to dry in air. Determine the distribution of radioactivity using suitable detector.

Not less than 95% of the radioactivity on the strip migrates towards the cathode as a single peak.

Chemical purity

Thallium. Transfer 1.0 ml of the injection and 1.0 ml of thallium standard (2 µg/ml Tl) TS to separate screw-cap test tubes. To each tube, add the following five solutions (A, B, C, D and E) and mix after each addition: 2 drops of a solution prepared by
carefully mixing 18 ml of nitric acid (~1000 g/l) TS and 82 ml of hydrochloric acid (~250 g/l) TS (solution A); 1.0 ml of sulfosalicylic acid (0.1 mol/l) VS (solution B); 2 drops of hydrochloric acid (~250 g/l) TS (solution C); 4 drops of a solution prepared by dissolving 50 mg of rhodamine B R in hydrochloric acid (~250 g/l) TS and diluting to 100.0 ml (solution D); 1.0 ml of diisopropyl ether R (solution E). Screw the caps on tightly, shake the tubes by hand for exactly 1 minute, releasing any pressure build-up by loosening the caps slightly. Recap the tubes and allow the phases to separate.

Transfer 0.5 ml of the ether layer from each tube to clean tubes. The color of the ether layer obtained from the injection is not darker than that from the thallium standard (2 µg/ml Tl) TS.

Iron. Into separate cavities of a spot plate, place 0.1 ml of the injection and 0.1 ml of iron standard TS diluted with water R to a concentration of 5 µg/ml. Add to each cavity 0.1 ml of a solution of hydroxylamine hydrochloride R (1 in 10), 1 ml of a solution of sodium acetate R (1 in 4), and 0.1 ml of a 0.5% dipyridyl solution prepared by dissolving 0.5 g of 2,2'-dipyridyl R in 100 ml of water R containing 0.15 ml of hydrochloric acid (~250 g/l) TS, and mix. After 5 minutes, the colour obtained from the injection is not darker than that of the iron standard solution.

Copper. Into separate cavities of a spot plate, place 0.2 ml of the injection and 0.2 ml of copper standard (5 µg/ml Cu) TS. Add to each cavity the following 3 solutions (A, B and C) and mix after each addition: 0.2 ml of water R (solution A) and 0.1 ml of a solution of iron thiocyanate prepared by dissolving 1.5 g of ferric chloride R and 2 g of potassium thiocyanate R in water R and diluting to 100.0 ml with the same solvent (solution B); 0.1 ml of a solution of sodium thiosulphate R (1 in 100) (solution C). The time required for the injection to decolorize is equal to or longer than that observed for the copper standard solution.

Radioactivity. Measure the radioactivity as described under R.1.1 Detection and measurement of radioactivity in suitable calibrated counting equipment by comparison with a standardized thallium-201 solution or by measurement in an instrument calibrated with the aid of such a solution.

Standardized thallium-201 solutions are available from laboratories recognized by the relevant national or regional authority.

Impurities
A. Lead-201
B. Lead-203
C. Thallium-200
D. Thallium-202
E. [²⁰¹Tl] Thallic (III) ion.

Biodistribution. Carry out the test as described under R3.1 Biological distribution using a set of three guinea pigs. At 1 hour post injection not less than 4% of the injected radioactivity should be found in the heart.