



# SULFADOXINE AND PYRIMETHAMINE TABLETS

## Revised draft proposal for *The International Pharmacopoeia* (September 2010)

### **REVISED DRAFT FOR COMMENT**

This document was provided by a quality control expert and was discussed at the recent WHO consultation on specifications for medicines and quality control laboratory issues. Previous comments received have been incorporated into this revised draft. Should you have any comments, please send these to Dr S. Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or e-mails: [kopps@who.int](mailto:kopps@who.int) with a copy to Ms C. Mendy [mendyc@who.int](mailto:mendyc@who.int) by 14 October 2010.

**In order to speed up the process for receipt of documents, please let us have your e-mail address (to [bonnyw@who.int](mailto:bonnyw@who.int)) which we will add to our electronic mailing list for monographs.**

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Dr Sabine Kopp, Quality Assurance Programme, Medicines Quality Assurance Programme, Quality & Safety: Medicines (QSM), Department of Essential Medicines and Pharmaceutical Policies (EMP), World Health Organization, CH-1211 Geneva 27, Switzerland. Fax: (41-22) 791 4730; e-mail: [kopps@who.int](mailto:kopps@who.int).

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**SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/07.218**  
*International Pharmacopoeia monograph on Sulfadoxine and Pyrimethamine tablets*

	<b>Date</b>
Preparation of first draft by laboratory	February 2007 –May 2007
First draft mailed out for comments	June 2007
Any comments received reviewed in Consultation on Specifications for Medicines and Quality Control Laboratory Issues	27-29 June 2007
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Collation of comments	August 2010
Comments discussed during video-/teleconference on specifications for medicines	25 August 2010
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Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations for possible adoption.	18-22 October 2010
Any further action as required	...

## **SULFADOXINE AND PYRIMETHAMINE TABLETS: Revised draft proposal for *The International Pharmacopoeia* (September 2010)**

**Category.** Antimalarial.

**Storage.** Sulfadoxine and pyrimethamine tablets should be kept in a well-closed container, protected from light.

**Additional information.** Strength in the current WHO Model list of essential medicines: 500 mg sulfadoxine and 25 mg pyrimethamine.

Strength in the current WHO Model list of essential medicines for children: 500 mg sulfadoxine and 25 mg pyrimethamine.

### **Requirements**

Comply with the monograph for "Tablets".

**Definition.** Sulfadoxine and pyrimethamine tablets contain Sulfadoxine and Pyrimethamine. They contain not less than 90.0% and not more than 110.0% of the amounts of sulfadoxine ( $C_{12}H_{14}N_4O_4S$ ) and pyrimethamine ( $C_{12}H_{13}ClN_4$ ) stated on the label.

### **Identity tests**

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

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 75 volumes of ethyl acetate R, 25 volumes of methanol R and 1 volume of glacial acetic acid R as the mobile phase. Apply separately to the plate 10  $\mu$ l of each of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets containing about 100 mg of Sulfadoxine for 5 minutes with 20 ml, filter, and use the filtrate. For solution (B) use 5 mg of sulfadoxine RS and 0.25 mg of pyrimethamine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

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

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Dip the plate in modified Dragendorff reagent TS. Examine the chromatogram in daylight.

The two principal spots obtained with solution A correspond in position, appearance, and intensity to those obtained with solution B (the spot due to pyrimethamine is faintly visible).

- B. See the test described under Assay. The retention times of the two principal peaks in the chromatogram obtained with solution (1) are similar to those in the chromatogram obtained with solution (4).

### Dissolution

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 1000 ml of hydrochloric acid (~4 g/l) TS, and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 5 ml of the medium through an in-line filter and use the filtrate. Determine the content of sulfadoxine ( $C_{12}H_{14}N_4O_4S$ ) and pyrimethamine ( $C_{12}H_{13}ClN_4$ ) in the filtrate according to the method as described under Assay and preparing solution (4) under Assay as follows: dilute 10.0 ml of solution (2) and 2.0 ml of solution (3) to 20.0 ml with hydrochloric acid (~4 g/l) TS.

For each of the six tablets, calculate the total amount of sulfadoxine ( $C_{12}H_{14}N_4O_4S$ ) and pyrimethamine ( $C_{12}H_{13}ClN_4$ ), in the medium from the results obtained. For both substances, the amount in solution for each tablet is not less than 80% of the amount declared on the label. For either substance, if the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 75% and no tablet contains less than 60%.

### Sulfadoxine-related substances

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 groups (5  $\mu$ m)<sup>1</sup>.

As the mobile phase, use a solution prepared as follows: dissolve 10 ml of glacial acetic acid R and 0.5 ml of triethylamine R in about 800 ml of water R, dilute to 1000 ml and adjust the pH to 4.2 by adding sodium hydroxide (~400 g/l) TS. Mix 850 ml of this solution with 120 ml of acetonitrile R and 30 ml of methanol R.

For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powder containing about 200 mg of Sulfadoxine into a 100-ml volumetric flask. Add 35 ml of acetonitrile R and sonicate for about 10 minutes. Allow to cool to room temperature and make up to volume with mobile phase. Filter a portion of this solution through a 0.45- $\mu$ m filter, discarding the first few ml of the filtrate. For solution (2) dilute 1 ml of solution (1) to 200 ml with the mobile phase.

For solution (3) prepare a solution containing about 1 mg of sulfadoxine RS and about 0.5 mg of sulfamethoxazole R per ml in acetonitrile R. Dilute 10 ml of this solution to 100 ml with the mobile phase.

Operate with a flow rate of 2 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 270 nm.

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<sup>1</sup> Phenomenex Luna® is suitable.

Inject separately 100 µl each of solutions (1), (2) and (3). Record the chromatograms for about 3.5 times the retention time of sulfadoxine (to ensure that pyrimethamine is eluted).

In the chromatogram obtained with solution (1), the following impurity peaks, if present, are eluted at the following relative retention with reference to sulfadoxine (retention time about 18 minutes): impurity A (sulfanilamide) about 0.1, impurity B about 0.2, impurity D about 0.3, impurity C about 1.4. A peak due to pyrimethamine has a relative retention of about 2.7. The test is not valid unless in the chromatogram obtained with solution (3), the resolution between the peaks due to sulfadoxine and to sulfamethoxazole (with relative retention of about 1.1 with reference to sulfadoxine) is at least 2.

In the chromatogram obtained with solution (1) the area of any peak, other than the peaks due to sulfadoxine and to pyrimethamine, is not greater than the area of the peak due to sulfadoxine in the chromatogram obtained with solution (2) (0.5%). The sum of the areas of all peaks, other than the peaks due to sulfadoxine and pyrimethamine, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

*[Note from Secretariat: in accordance with WHO's guideline on the development of fixed-dose combinations dosage forms (least stable API controlled), and considering the ratio between the two APIs in the formulation which is 1 to 20, a test for related substances is only proposed for sulfadoxine.]*

#### **Assay**

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

As the mobile phase, use a solution prepared as follows: dissolve 10 ml of glacial acetic acid R and 0.5 ml of triethylamine R in about 800 ml of water R, dilute to 1000 ml and adjust the pH to 4.2 by adding sodium hydroxide (~400 g/l) TS. Mix 800 ml of this solution with 200 ml of acetonitrile R.

For solution (1) weigh and powder 20 tablets and transfer a quantity of the powder containing about 0.50 g of Sulfadoxine, accurately weighed, into a 200-ml volumetric flask. Add about 70 ml of acetonitrile R and sonicate for 10 minutes. Allow to cool to room temperature, make up to volume using the mobile phase and sonicate for 10 minutes. Dilute 5 ml of this solution to 25 ml with mobile phase and filter a portion of this solution through a 0.45-µm filter, discarding the first few ml of the filtered solution. For solution (2), transfer 25 mg of sulfadoxine RS, accurately weighed, to about 10 ml of acetonitrile R, sonicate until dissolved and dilute to 25.0 ml with the mobile phase. For solution (3), transfer 25 mg of pyrimethamine RS, accurately weighed, to about 35 ml of acetonitrile R, sonicate until dissolved and dilute to 100.0 ml with the mobile phase. For solution (4) dilute 10.0 ml of solution (2) and 2.0 ml of solution (3) to 20.0 ml with the mobile phase.

Operate with a flow rate of 2 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 227 nm.

Inject 20 µl of solution (4). The assay is not valid unless the resolution between the peaks due to sulfadoxine and to pyrimethamine, eluting in this order, is at least 5. The run time for the analyses is not less than 25 minutes.

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<sup>2</sup> Phenomenex Luna® is suitable.

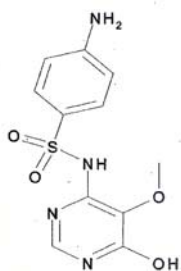
Inject alternately 20  $\mu$ l each of solutions (1) and (4).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (4), and calculate the content of sulfadoxine ( $C_{12}H_{14}N_4O_4S$ ) and pyrimethamine ( $C_{12}H_{13}ClN_4$ ) in the tablets.

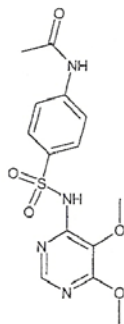
### Impurities

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

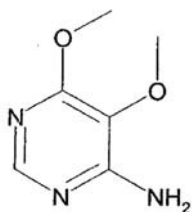
#### A. sulfanilamide



#### B. N1-(6-hydroxy-5-methoxy-4-pyrimidinyl) sulfanilamide



#### C. 4-(p-acetamido-benzosulfonamido)-5,6-dimethoxy-pyrimidine



#### D. 4-Amino-5,6-dimethoxy-pyrimidine.

[*Note from Secretariat: structures and chemical names for related substances to be confirmed.*]

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**New reagent to be added to Ph.Int.**

**Sulfamethoxazole R.** *N'*-(5-Methyl-3-isoxazolyl)sulfanilamide: 4-amino-*N*-(5-methyl-3-isoxazolyl)benzenesulfonamide; C<sub>10</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S

A commercially available reagent of suitable grade.

*Description.* A white or yellowish white, crystalline powder.

*Solubility.* Very slightly soluble in water; soluble in 50 parts of ethanol (~750 g/l) TS and in 3 parts of acetone R.

**Hydrochloric acid (~4 g/l) TS.**

Dilute 10 ml of hydrochloric acid (~420 g/l) TS with sufficient water to produce 1000 ml (approximately 0.1 mol/l).

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Revised draft for comment