GENERAL INFORMATION

1. Aristolochic acid

Aristolochic acid, which occurs in plants of *Aristolochiaceae*, is suspected to cause renal damage. It is also reported to have oncogenicity (see References).

There will be no problem when crude drugs of the origin designated in the JP are used, but there may be differences in crude drug nomenclature between different countries, and it is known that crude drug preparations not meeting the specifications of the JP are circulating in some countries. Consequently, when crude drugs or their preparations are used, it is important that the materials should not include any plants containing aristolochic acid.

Crude drugs for which particular care is necessary are as follows:

Asiasarum root, Akebia stem, Sinomenium stem, and Saussurea root.

References:

Drug & Medical Device Safety Information (No.161) (July, 2000); New England Journal of Medicine (June 8, 2000)

An example of an assay method for aristolochic acid is as follows:

Assay—

1) Preparation of sample solution To 2.0 g of powdered material to be tested add 50 mL of a mixture of methanol and water (3:1), shake for 15 minutes (if an ultrasonicator is used, for 20 minutes), filter, and use the filtrate as the sample solution.

2) Preparation of standard solution Weigh exactly X mg [1] of aristolochic acid, equivalent to 10 mg of aristolochic acid I, and dissolve in a mixture of methanol and water (3:1) to make exactly 200 mL. Pipet 2 mL of this solution, add a mixture of methanol and water (3:1) to make exactly 250 mL, and use this solution as the standard solution.

Note 1): X mg $= 10 \times 100/F$, where F is the labeled amount (%) of aristolochic acid I.

3) Standard procedure and assessment of result Perform the test with exactly 10 μL each of the sample solution and the standard solution, according to the following conditions, as directed under the Liquid chromatography. The sample is acceptable if the sample solution shows no peak at the retention time corresponding to aristolochic acid I from the standard solution. If the sample shows such a peak, repeat the test under different conditions: if the sample no longer shows a peak at a retention time that coincides with that of standard aristolochic acid under the new conditions, the sample is acceptable.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 400 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of between 25°C and 40°C.

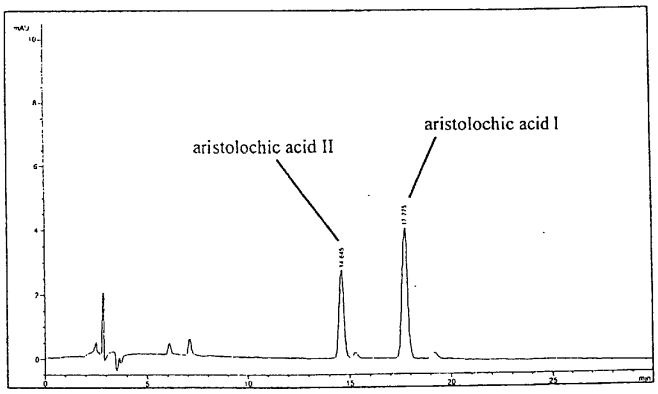
Mobile phase: A mixture of 0.05 mol/L NaH_2PO_4 (H_3PO_4 2 mL)[2] and CH_3CN (11:9).

Flow rate: 1.0 mL/min

Note 2): To 7.8 g of sodium dihydrogenphosphate dihydrate and 2 mL of phosphoric acid add water to make 1000 mL.

4) Others The operating conditions may be changed within the limits described under the Liquid chromatography.

5) Chromatogram of aristolochic acid (reference substance) A chromatogram of aristolochic acid obtained under the operating conditions described in 3) Standard procedure and assessment of result is shown below:



2. Decision of Limit for Bacterial Endotoxins

The endotoxin limit for injections is to be decided as follows:

$$\text{Endotoxin limit} = K/M$$

where K is a minimum pyrogenic dose of endotoxin per kg body mass (EU/kg), and M is equal to the maximum dose of product per kg per hour.

M is expressed in mL/kg for products to be administered by volume, in mg/kg or mEq/kg for products to be administered by mass, and in Unit/kg for products to be administered by biological units. Depending on the administration route, values for K are set as in the following table.

Intended route of administration	K (EU/kg)
Intravenous	5.0
Intravenous, for radiopharmaceuticals	2.5
Intraspinal	0.2