British Pharmacopoeia

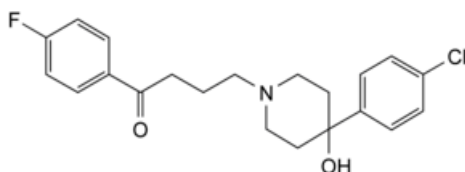**Quality standards**

> Edition: BP 2025 (Ph. Eur. 11.6 update)

Haloperidol

[General Notices](#)

(Ph. Eur. monograph 0616)

$C_{21}H_{23}ClFNO_2$ 375.9   *52-86-8*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparations

[Haloperidol Capsules](#)

[Haloperidol Injection](#)

[Haloperidol Oral Solution](#)

[Haloperidol Tablets](#)

Ph Eur

DEFINITION

4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent), in methanol and in methylene chloride.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Melting point (*2.2.14*): 150 °C to 153 °C.
B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison   haloperidol CRS.

C. Thin-layer chromatography (*2.2.27*).

Test solution   Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a)   Dissolve 10 mg of *haloperidol CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b)   Dissolve 10 mg of *haloperidol CRS* and 10 mg of *bromperidol CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate   TLC octadecylsilyl silica gel plate R.

Mobile phase   tetrahydrofuran R, *methanol R*, 58 g/L solution of *sodium chloride R* (10:45:45 *V/V/V*).

Application   1 µL.

Development   In an unsaturated tank, over 2/3 of the plate.

Drying   In air.

Detection   Examine in ultraviolet light at 254 nm.

System suitability   Reference solution (b):

— the chromatogram shows 2 spots which may, however, not be completely separated.

Results   The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 10 mg in 5 mL of *anhydrous ethanol R*. Add 0.5 mL of *dinitrobenzene solution R* and 0.5 mL of *2 M alcoholic potassium hydroxide R*. A violet colour is produced and becomes brownish-red after 20 min.
E. To 0.1 g in a platinum crucible add 0.5 g of *anhydrous sodium carbonate R*. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 5 mL of *dilute nitric acid R* and filter. To 1 mL of the filtrate add 1 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Dissolve 0.2 g in 20 mL of a 1 per cent *V/V* solution of *lactic acid R*.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use and protect from light.*

Test solution   Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a)   Dissolve 10 mg of *haloperidol for system suitability CRS* (containing impurities B and D) in 1.0 mL of *methanol R*.

Reference solution (b)   Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c)   Dissolve 10 mg of *haloperidol for peak identification CRS* (containing impurities G and H) in 1.0 mL of *methanol R*.

Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: 17 g/L solution of *tetrabutylammonium hydrogen sulfate R1*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 17	90 → 50	10 → 50
17 - 22	50	50

Flow rate   1.5 mL/min.

Detection   Spectrophotometer at 230 nm.

Injection   10 µL.

Identification of impurities   Use the chromatogram supplied with *haloperidol for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and D; use the chromatogram supplied with *haloperidol for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities G and H.

Relative retention   With reference to haloperidol (retention time = about 8 min): impurity B = about 0.9; impurity D = about 1.6; impurity G = about 1.8; impurity H = about 2.0.

System suitability   Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity B and haloperidol.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 0.7;

— *impurity D*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities G, H*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 37.59 mg of $C_{21}H_{23}ClFNO_2$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities   B, D, G, H.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use)   A, C, E, F.
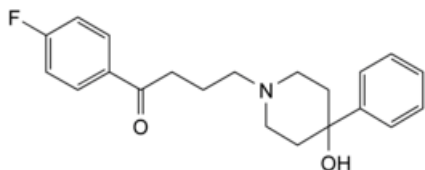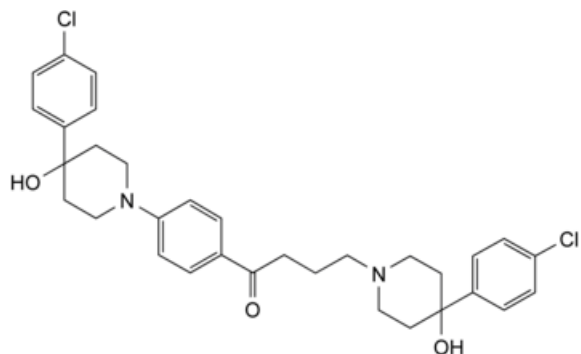

A.   1-(4-fluorophenyl)-4-(4-hydroxy-4-phenylpiperidin-1-yl)butan-1-one,
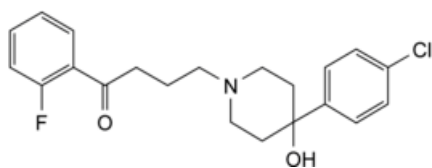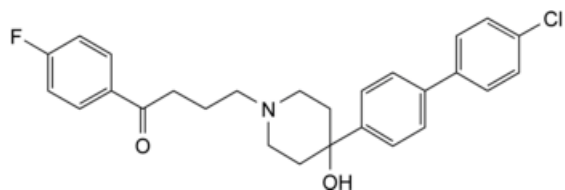

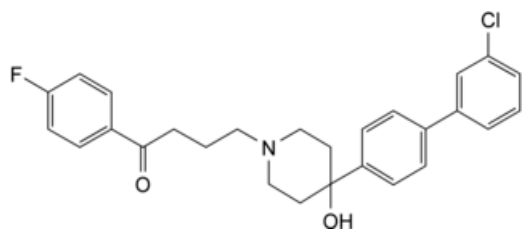B.   4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(2-fluorophenyl)butan-1-one,
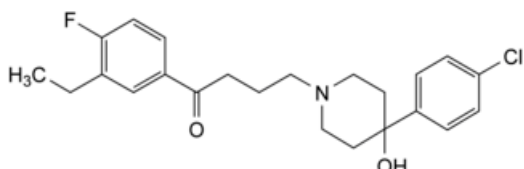
C.   4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(3-ethyl-4-fluorophenyl)butan-1-one,

D.   4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-[4-[4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]phenyl]butan-1-one,

E.   4-[4-(4′-chlorobiphenyl-4-yl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one,

F.   4-[4-(3′-chlorobiphenyl-4-yl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one,

G.   unknown structure,

H.   unknown structure.

Ph Eur