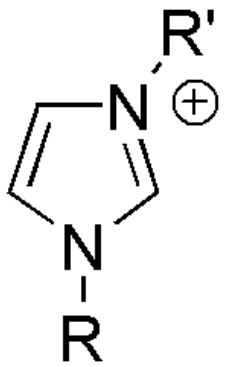
МЕДИЦИНСКИ УНИВЕРСИТЕТ – ПЛЕВЕН
ФАКУЛТЕТ „ФАКУЛТЕТ ФАРМАЦИЯ“
ЦЕНТЪР ЗА ДИСТАНЦИОННО ОБУЧЕНИЕ

Лекция №05

# Анализ на антиинфекциозни лекарства. Производни на имидазола, фурана, индола и акридина – 1 част

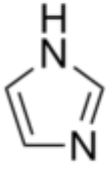
проф. Данка Обрешкова, дм, дфн

# АНАЛИЗ НА ЛЕКАРСТВА – ИМИДАЗОЛОВИ И ИМИДАЗОЛИНОВИ ПРОИЗВОДНИ

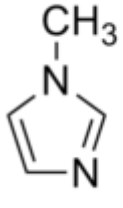



Imidazole is amphoteric, *i.e.*, it can function as both an acid and as a base. As an acid, the p*K*a of imidazole is 14.5, making it less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. The acidic proton is located on N-1. As a base, the p*K*a of the conjugate acid (cited above as p*K*BH+ to avoid confusion between the two) is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic site is N-3.

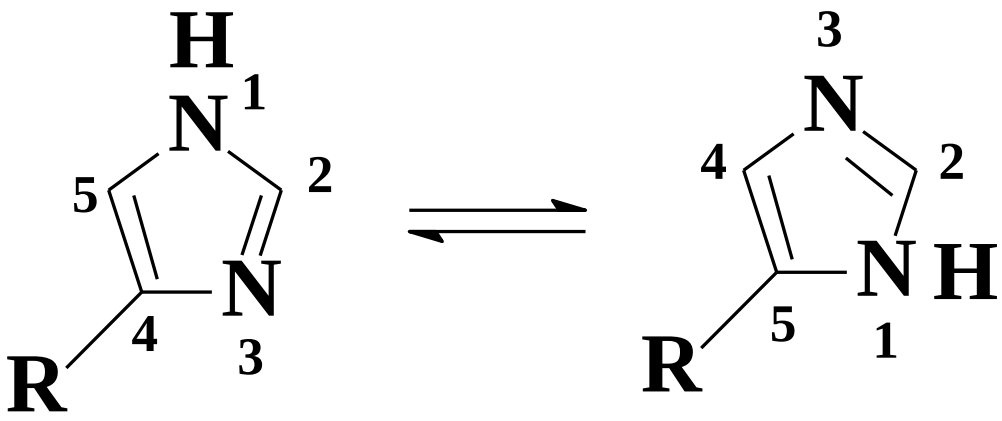
pyrrole-like nitrogen, $pK_a = 14.5$

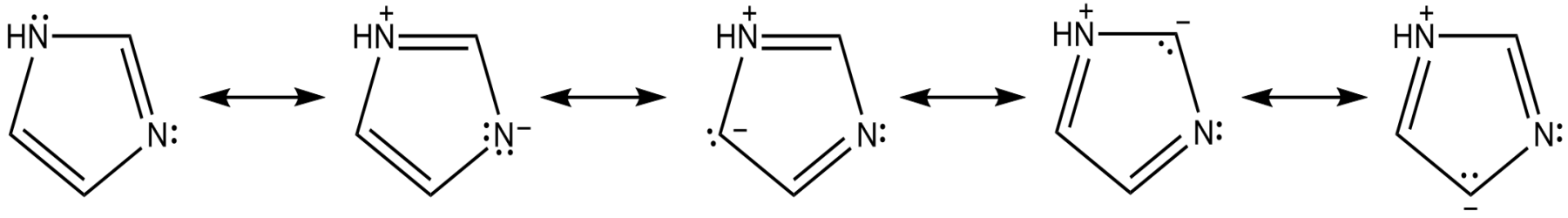


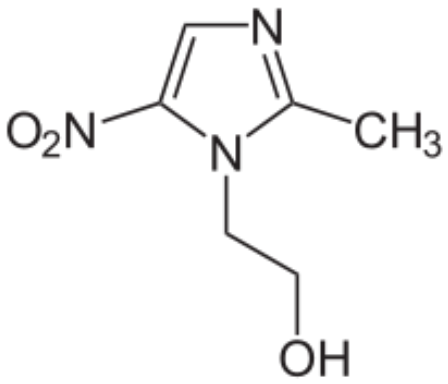

pyridine-like nitrogen, $pK_a = 7.0$



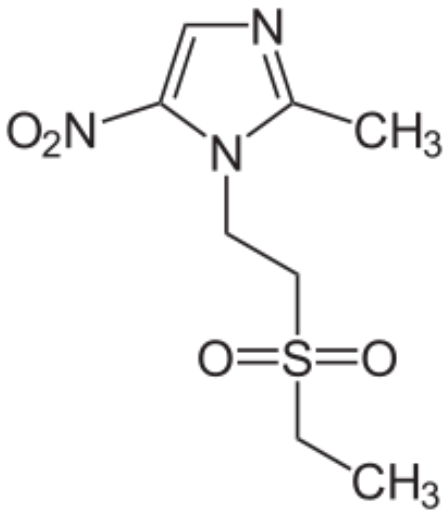

pyridine-like nitrogen, $pK_a = 7.4$


H
N
1
2
5
N
4
3
R
3
N
4
2
N
H
5
1
R

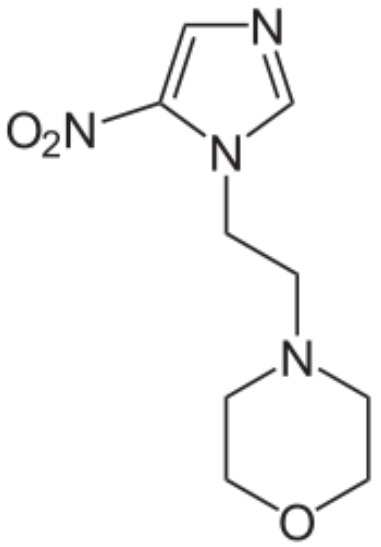

HN
N:
HN
N
HN
N:
HN
N:
HN
N:




Metronidazole




Tinidazole




Nimorazole

**Тест за идентичност:**

***Реакция за първична ароматна амино група след редукция на нитро групата***. Реакцията е с ниска специфичност (напр. при Tinidazole Impurity A (2-methyl-5-nitroimidazole) и Impurity B (1-(2-ethylsulfonylethyl)-2-methyl-4-nitroimidazole) съдържат ароматна нитро група като при Impurity B разликата е само в позицията на нитро групата);

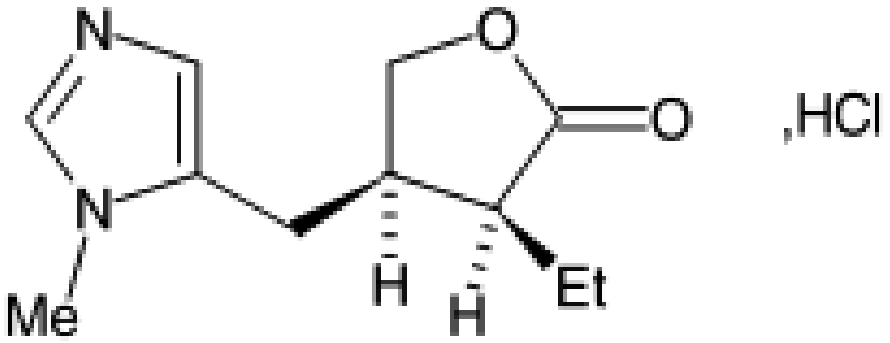
***т.т.; IR тест; TLC тест.***

**Тест за чистота:** ***BETX.***

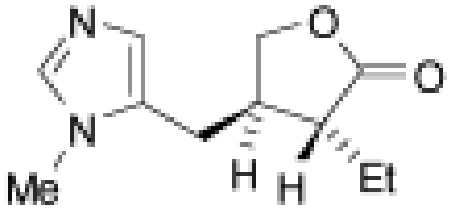
**Количествено съдържание:** ***Неводно титруване.***

# Pilocarpine HCl

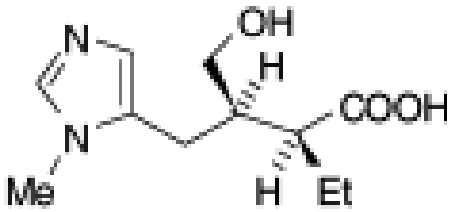
**(3*S*,4*R*)-3-ethyl-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]dihydrofuran-2(3*H*)one**



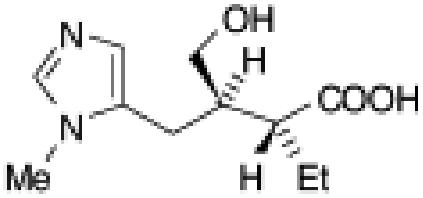

**isopilocarpine**



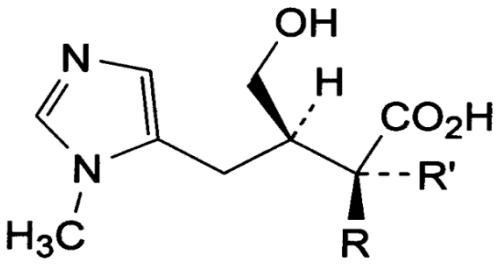

**pilocarpic acid**




**isopilocarpic acid**



# Pilocarpine




Examine by liquid chromatography *(2.2.29)*.

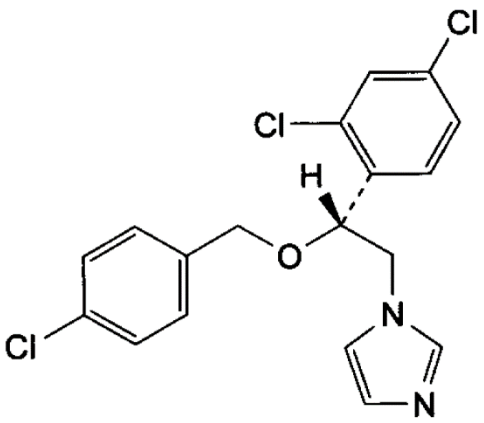
*Test solution* Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 100.0 ml with the same solvent.

*Reference solution (a)* Dilute 5.0 ml of the test solution to 100.0 ml with *water R*. Dilute 2.0 ml of the solution to 20.0 ml with *water R*.

*Reference solution (b)* Dissolve 5.0 mg of *pilocarpine nitrate for system suitability CRS* in *water R* and dilute to 50.0 ml with the same solvent.

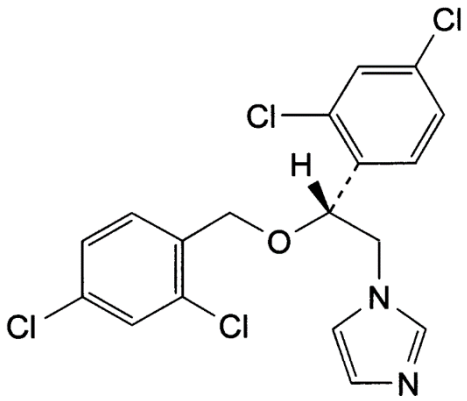
*Reference solution (c)* To 5 ml of the test solution, add 0.1 ml of *ammonia R* and heat the solution on a water-bath for 30 min, cool and dilute to 25 ml with *water R*. Take 3 ml of this solution and dilute to 25 ml with *water R*. Mainly **pilocarpic acid** is formed.

**Econazole**

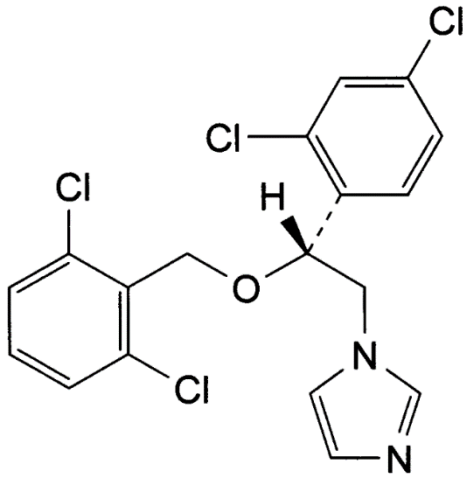



and enantiomer

**Miconazole**




and enantiomer




and enantiomer

**Isoconazole**

The chromatographic procedure may be carried out using:

—a stainless steel column 0.1 m long and 4.6 mm in internal diameter packed with ***octadecylsilyl silica gel*** *for chromatography R* (3 µm),

—as mobile phase at a flow rate of 2 ml/min a solution of 6.0 g of ***ammonium acetate R* in a mixture of 300 ml of *acetonitrile R*, 320 ml of *methanol R* and 380 ml of *water R*,**

—as detector a spectrophotometer set at **235 nm**.

| | | |
|---|---|---|
| **Isoconazole**<br><br>**Isoconazole Nitrate** | **1-[(2*RS*)-2-[(2,6-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole** | ***УВ-mecm - $\lambda_{max}$, $A_{1\%, 1cm}$*** |
| **Econazole**<br><br>**Econazole Nitrate** | **1-[(2*RS*)-2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole** | ***УВ-mecm, ratio of absorbance – 271 / 280 – 1.5 – 1.7*** |
| **Miconazole**<br><br>**Miconazole Nitrate** | **1-[(2*RS*)-2-[(2,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole** | ***УВ-mecm - $\lambda_{max}$, $A_{1\%, 1cm}$*** |

***Ph Eur***

# Econazole, Isoconazole, Miconazole

## ASSAY of Econazole

Dissolve 0.300 g in 75 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically *(2.2.20)*. Carry out a blank titration.

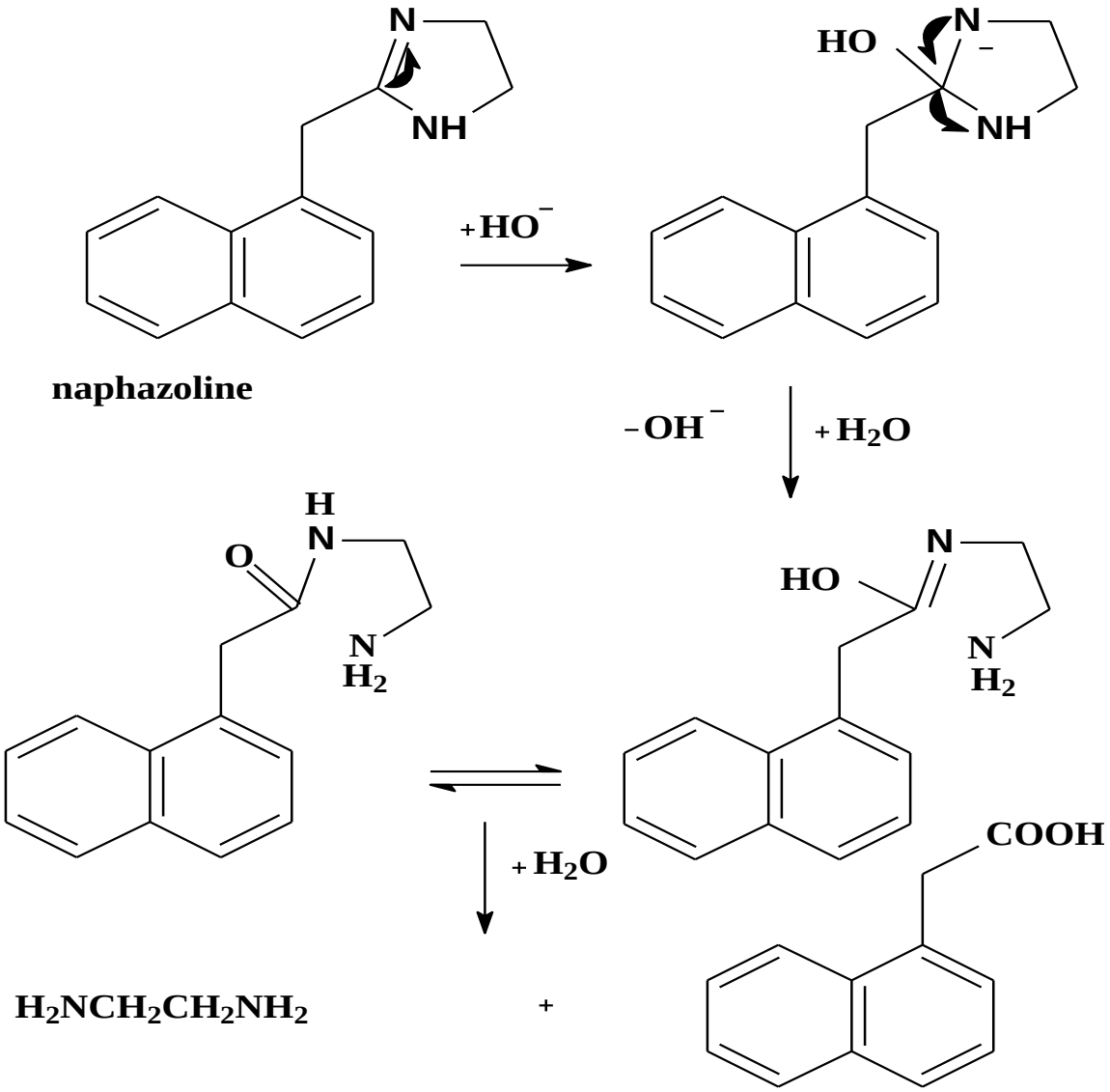
## Related substances of Isoconazole

Examine by liquid chromatography. *Reference solution (a)* Dissolve 2.5 mg of *isoconazole CRS* and 2.5 mg of *econazole nitrate CRS* in the mobile phase and dilute to 100.0 ml with the mobile phase.

## Identification of Miconazole nitrate cream

A. Mix a quantity containing 40 mg of Miconazole Nitrate with 20 ml of a mixture of 1 volume of 1M *sulphuric acid* and 4 volumes of *methanol* and shake with two 50 ml quantities of *hexane*, discarding the organic layers. Make the aqueous phase alkaline with 2M *ammonia* and extract with two 40 ml quantities of *chloroform*. Combine the chloroform extracts, shake with 5 g of *anhydrous sodium sulphate*, filter and dilute the filtrate to 100 ml with *chloroform*. Evaporate 50 ml to dryness and dissolve the residue in 50 ml of a mixture of 1 volume of 0.1M *hydrochloric acid* and 9 volumes of *methanol* . The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits maxima at 264, 272 and 280 nm.

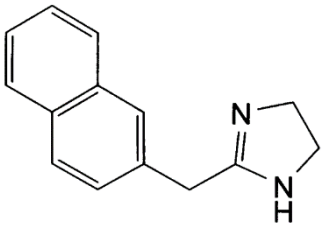
# Naphazoline




1-naphthylacetic acid

# Naphazoline Impurities

**2-(naphthalen-2-ylmethyl)-4,5-dihydro-1*H*-imidazole (β-naphazoline)**




Liquid chromatography *(2.2.29)*.

***Test solution*** Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 ml with the mobile phase.

***Reference solution (a)*** Dissolve 5 mg of *1-naphthylacetic acid R* in the mobile phase, add 5 ml of the test solution and dilute to 100 ml with the mobile phase.

***Reference solution (b)*** Dissolve 5.0 mg of *naphazoline impurity A CRS* in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 1.0 ml to 100.0 ml with the mobile phase.

*Reference solution (c)* Dilute 1.0 ml of the test solution to 10.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 100.0 ml with the mobile phase.

***Column:***

—*stationary phase*: *base-deactivated end-capped octylsilyl silica gel for chromatography R* (4 µm) with a pore size of 6 nm.

***Mobile phase*** Dissolve 1.1 g of *sodium octanesulphonate R* in a mixture of 5 ml of *glacial acetic acid R*, 300 ml of *acetonitrile R* and 700 ml of *water R*. *Flow rate* 1 ml/min.

***Detection*** Spectrophotometer at 280 nm.

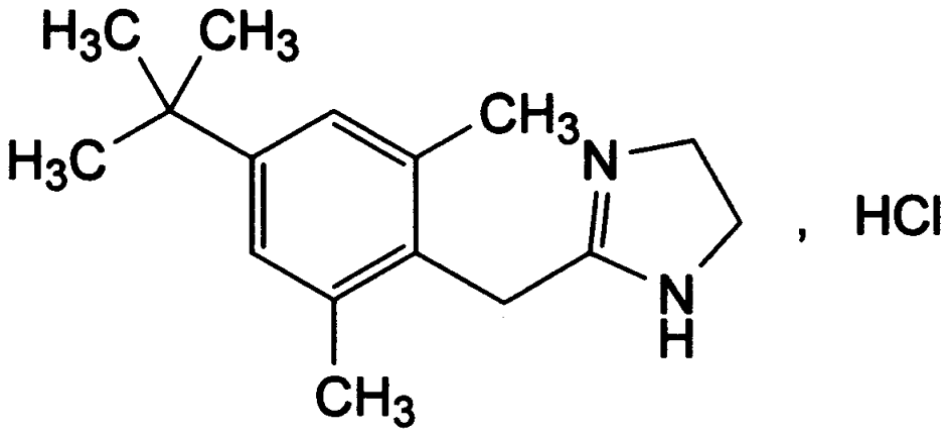
*Retention time* Naphazoline = about 14 min.

***System suitability*** Reference solution (a):

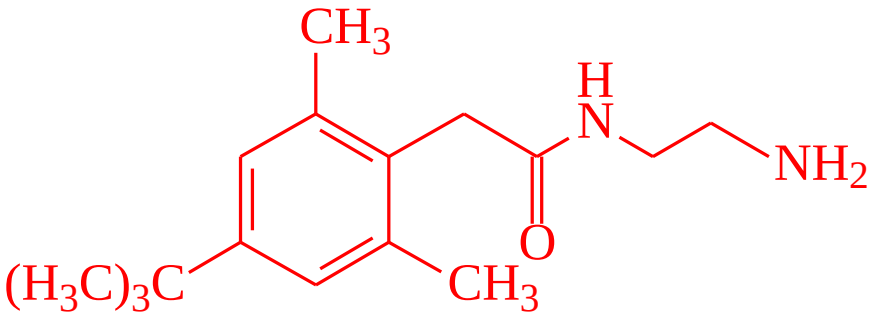
—*resolution*: minimum 5.0 between the peaks due to naphazoline and to impurity B.

*Limits*

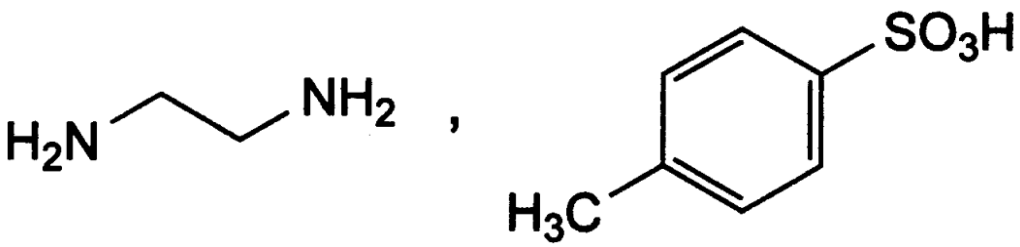
# Xylometazoline



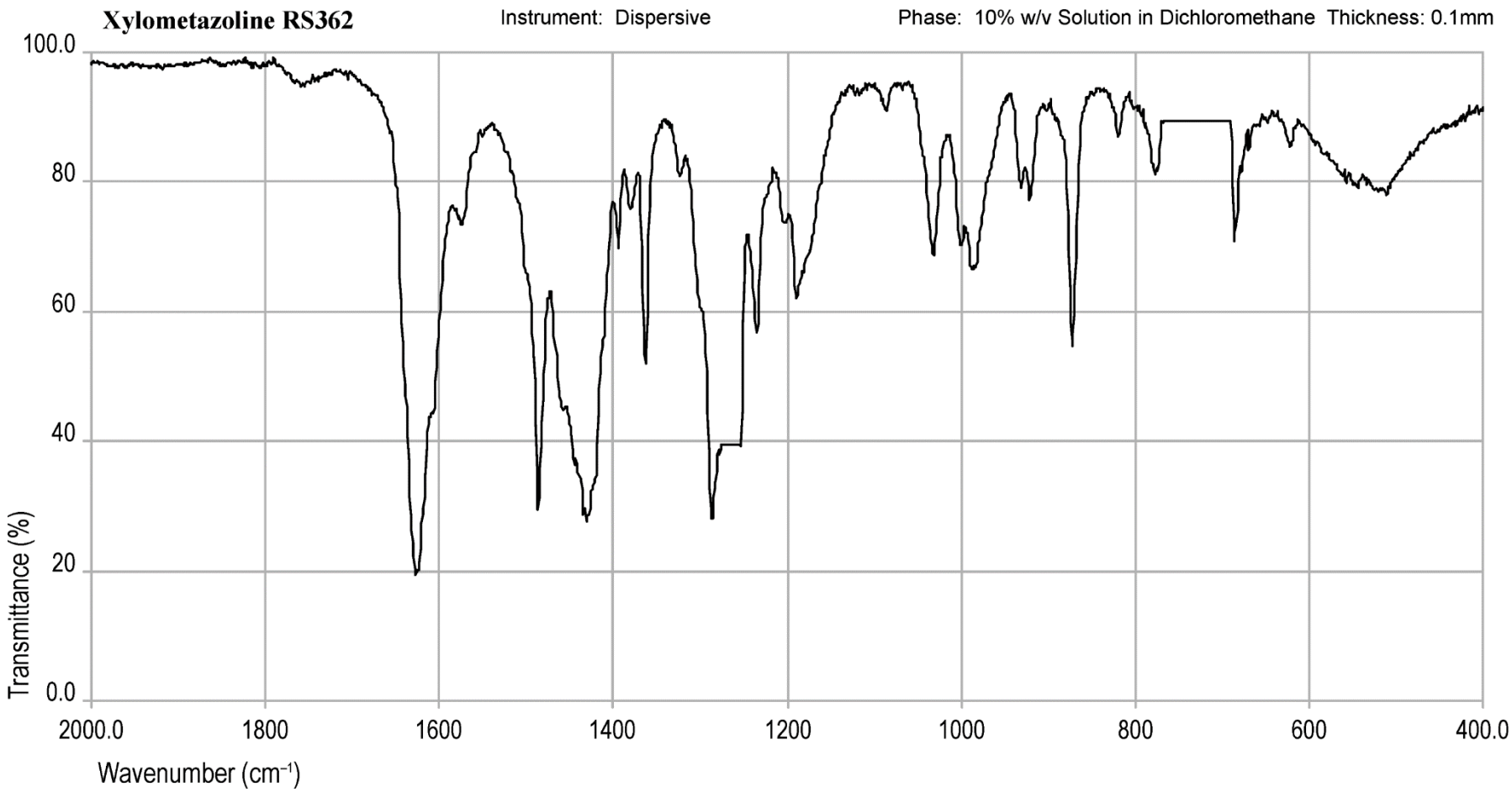

**2-[4-(1,1-Dimethylethyl)-2,6-dimethylbenzyl]-4,5-dihydro-1*H*-imidazole hydrochloride**




***N*-(2-aminoethyl)-2-[4-(1,1-dimethylethyl)-2,6-dimethylphenyl]acetamide**

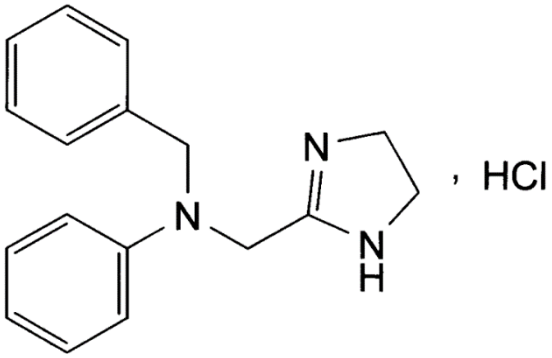



**ethane-1,2-diamine mono(4-methylbenzenesulphonate)**



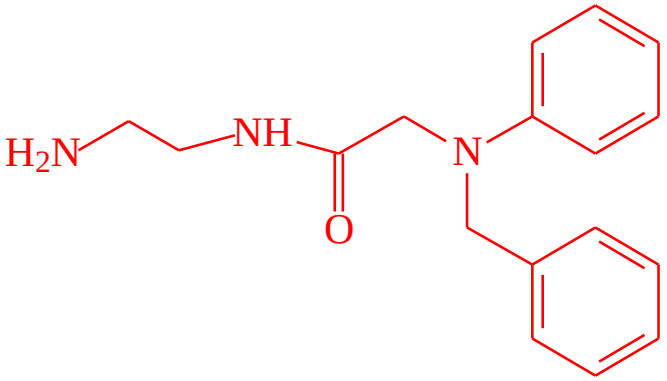

**C=N stretching frequency usually is observed at about 1650 $cm^{-1}$. The N-H group which give absorptions in the same region also could affect the C=N stretching frequency due to coupling.**
**The band at 1500 cm-1 is assigned to the N-H deformation vibration.**

# Antazoline




***N*-benzyl-*N*-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]aniline hydrochloride**

**IMPURITY**



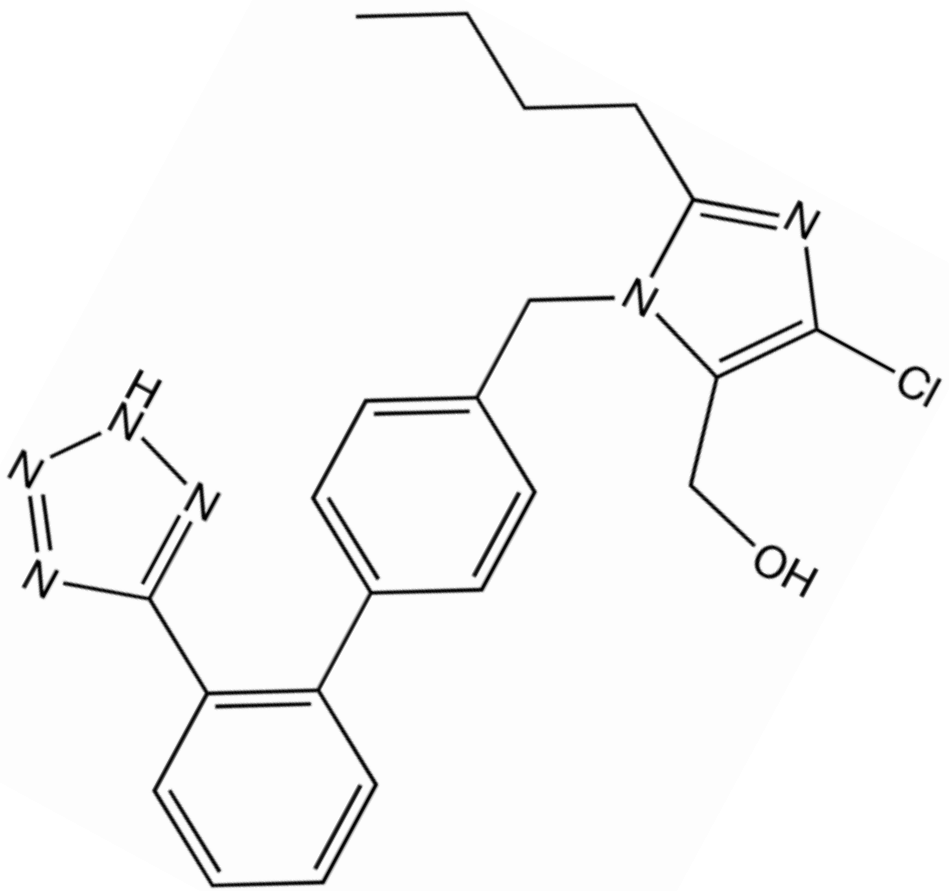

***N*-(2-aminoethyl)-2-(benzylphenylamino)acetamide**

**ASSAY**

**Dissolve 0.250 g in 100 ml of *alcohol R*. Add 0.1 ml of *phenolphthalein solution R1*. Titrate with *0.1 M alcoholic potassium hydroxide*.**

**1 ml of *0.1 M alcoholic potassium hydroxide* is equivalent to 30.18 mg of $C_{17}H_{20}ClN_3$.**

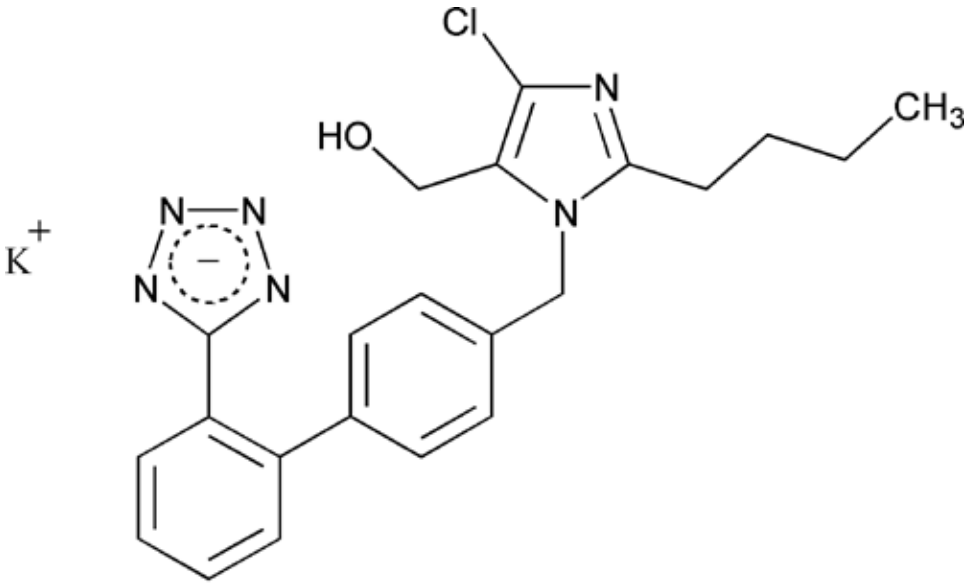
# *Losartan*




(1-((2'-(2*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-
2-butyl-4-chloro-1*H*-imidazol-5-yl)methanol

USP 28–NF 23
through *First Supplement*
Official 4/1/05 - 7/31/05

# *Losartan*




**Identification**

**A:** ***Infrared Absorption*** 197M—

**B:** ***Ultraviolet Absorption*** 197U—

*Solution:* 10 µg per mL.

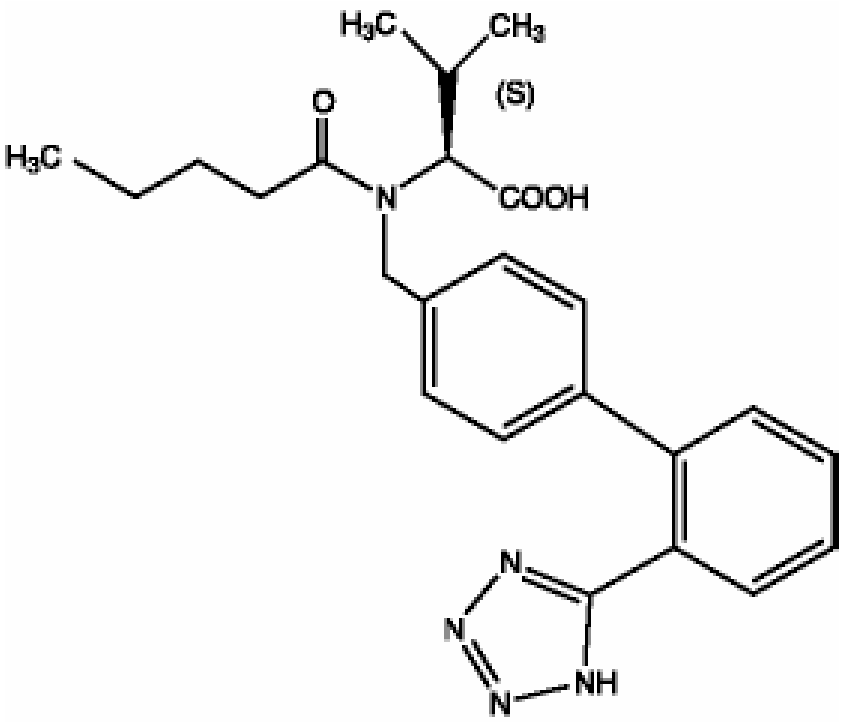
*Medium:* methanol.

**C:** It meets the requirements of the test for *Potassium* 191.

**Water,** *Method I* 921**:** not more than 0.5%.

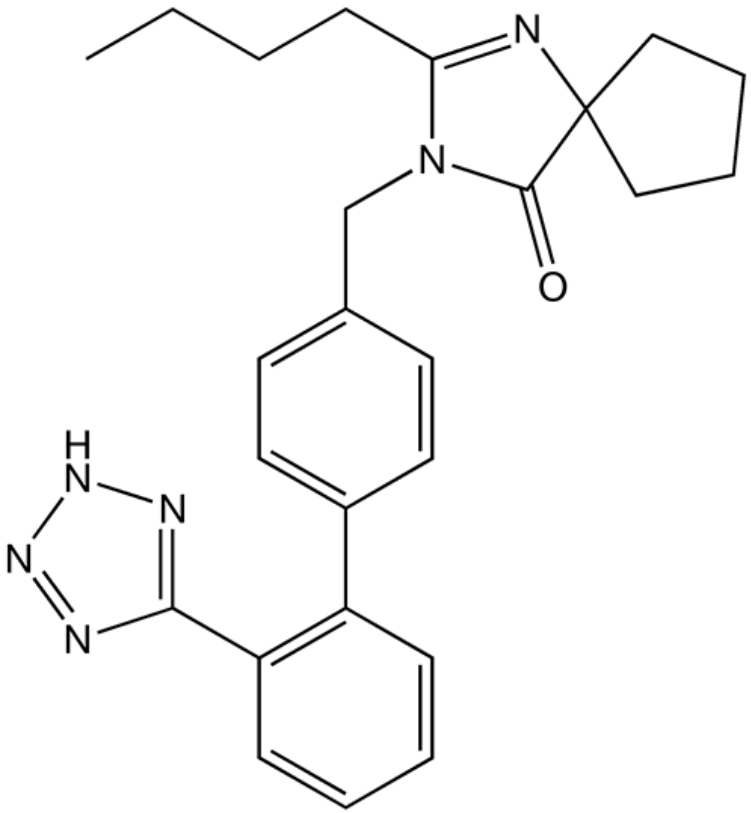
**HPLC Measurements**. Samples were analyzed according to the laboratory standard, HPLC (La-Chrom®, Merck-Hitachi, Darmstadt, Germany) with a diode array detector and a Purospher® STAR RP-18 endcapped column (125-4, 5 µm; Merck, Darmstadt, Germany). The eluent was 45% acetonitril/55% H2O with 0.1% trifluoroacetic acid (pH 1.9) for **losartan and valsartan** and 15% acetonitril/85% $H_2O$ with 0.1% trifluoroacetic acid (pH 1.9) for cefadroxil. UV-detection was done at 232 nm, the injection volume was 20 µl, the flow rate 0.75 ml/min and the column temperature 34°C. Cephalexin was used as internal standard for cefadroxil whereas losartan was used as internal standard for valsartan and vice versa. The retention time were between 2.5 and 8 min.

# Valsartan

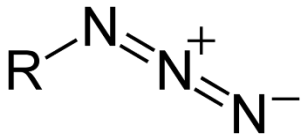



*N*-(1-oxopentyl)-*N*-[[2′-(1*H*-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-L-valine

# Irbesartan




2-butyl-3-[*p*-(*o*-1*H*-tetrazol -5-ylphenyl) benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one





**Limit of azide—**

*Mobile phase*— Prepare a filtered and degassed 0.1 N sodium hydroxide solution (see *System Suitability* under *Chromatography* ⟨621⟩).

*Standard solution*— Transfer about 25 mg of sodium azide, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 250 µL of this solution into a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. This solution contains about 0.312 µg of sodium azide per mL.

*Test solution*— Transfer about 100 mg of ***Irbesartan***, accurately weighed, to a 5-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

*Chromatographic system* (see *Chromatography* ⟨621⟩)— The liquid chromatograph is equipped with a conductimetric detector, and a 4.0-mm × 25-cm column that contains packing L46. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the signal to noise ratio for the azide peak is not less than 10.

*Procedure*— Separately inject equal volumes (about 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak area for azide peak. Calculate the amount of azide in ppm in the portion of Irbesartan taken by the formula:

$$1000(CS / CT)(42.02/65.01)(rU / rS),$$

in which *CS* is the concentration, in µg per mL, of sodium azide in the *Standard solution; CT* is the concentration, in mg per mL, of Irbesartan in the *Test solution; rU* is the peak area for azide obtained from the *Test solution;* and *rS* is the peak area for azide obtained from the *Standard solution:* not more than 10 ppm of azide is found.

EMEA/H/C/786

**ЕВРОПЕЙСКИ ДОКЛАД ЗА ОБЩЕСТВЕНА ОЦЕНКА (EPAR)**

**IRBESARTAN BMS**

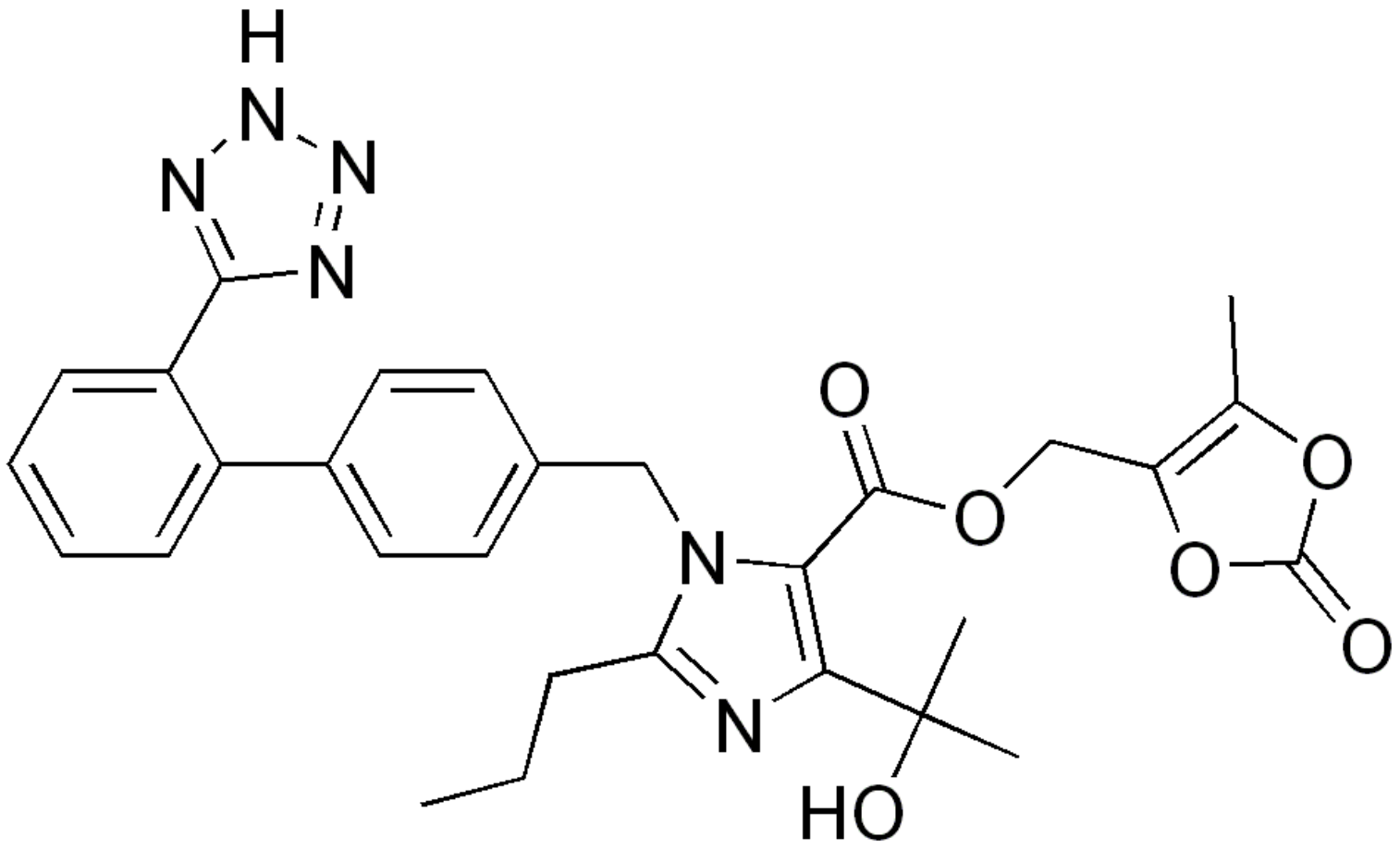
**Резюме на EPAR за обществено ползване**

*Настоящият документ представлява резюме на Европейския доклад за обществена оценка (EPAR). В него се разяснява как Комитетът по лекарствените продукти за хуманна употреба (CHMP) оценява проведените проучвания, за да направи своите препоръки как да се използва лекарството.*

*Ако се нуждаете от повече информация за Вашето медицинско състояние или лечение, прочетете листовката (също част от EPAR) или попитайте Вашия лекар или фармацевт. Ако желаете повече информация за основанията на препоръките на CHMP, прочетете научното обсъждане (също част от EPAR).*

**Какво представлява Irbesartan BMS?**
Irbesartan BMS е лекарство, което съдържа активното вещество ирбесартан. Предлага се под формата на бели овални таблетки (75, 150 и 300 mg).
Това лекарство е същото като Karvea, което вече е одобрено в Европейския съюз (ЕС). Компанията производител на Karvea е дала съгласие научните й данни да се използват за Irbesartan BMS.
**За какво се използва Irbesartan BMS?**
Irbesartan BMS се използва при пациенти с есенциална хипертония (високо кръвно налягане). „Есенциална“ означава, че високото кръвно налягане не е причинено от други заболявания. Irbesartan BMS се използва също за лечение на ренални (бъбречни) заболявания при пациенти с хипертония и диабет тип 2 (неинсулино-зависим диабет). Употребата на Irbesartan BMS не се препоръчва при пациенти на възраст под 18 години.
Лекарствен продукт, отпускан по лекарско предписание.
**Как да използвате Irbesartan BMS?**
Irbesartan BMS се приема през устата със или без храна. Обичайната препоръчвана доза е 150 mg веднъж на ден. Ако не се постигне достатъчен контрол на кръвното налягане, дозата може да бъде увеличена до 300 mg на ден или да се добавят други лекарства за хипертония, например хидрохлоротиазид. При пациенти на хемодиализа (техника за перчистване на кръвта) или при пациенти на възраст над 75 години може да се прилага начална доза от 75 mg.
При пациенти с хипертония и диабет тип 2 Irbesartan BMS се добавя към другите лечения на хипертония. Лечението започва със 150 mg веднъж на ден и дозата обикновено се увеличава до 300 mg веднъж на ден.
**Как действа Irbesartan BMS?**
Активното вещество в Irbesartan BMS, ирбесартан, е „ангиотензин-II рецепторен антагонист“, което означава, че блокира действието на хормона в организма, наречен ангиотензин II. Ангиотензин-II е мощен вазоконстриктор (вещество, което свива кръвоносните съдове). Като блокира рецепторите, с които нормално се свързва ангиотензин II, ирбесартан спира действието на хормона и позволява на кръвоносните съдове да се разширят. Това позволява кръвното налягане да се понижи и намалява рисковете от увреждания, причинени от високото кръвно налягане, например получаване на удар.

## *Olmesartan*




(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 5-(2-hydroxypropan-2-yl)-2-propyl-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]imidazole-4-carboxylate