Substances in the European Pharmacopoeia (Ph. Eur.)

Dr Hans-Joachim Bigalke, EDQM, Council of Europe

GInAS Summer Meeting -

Uppsala, Sweden

7 September 2015

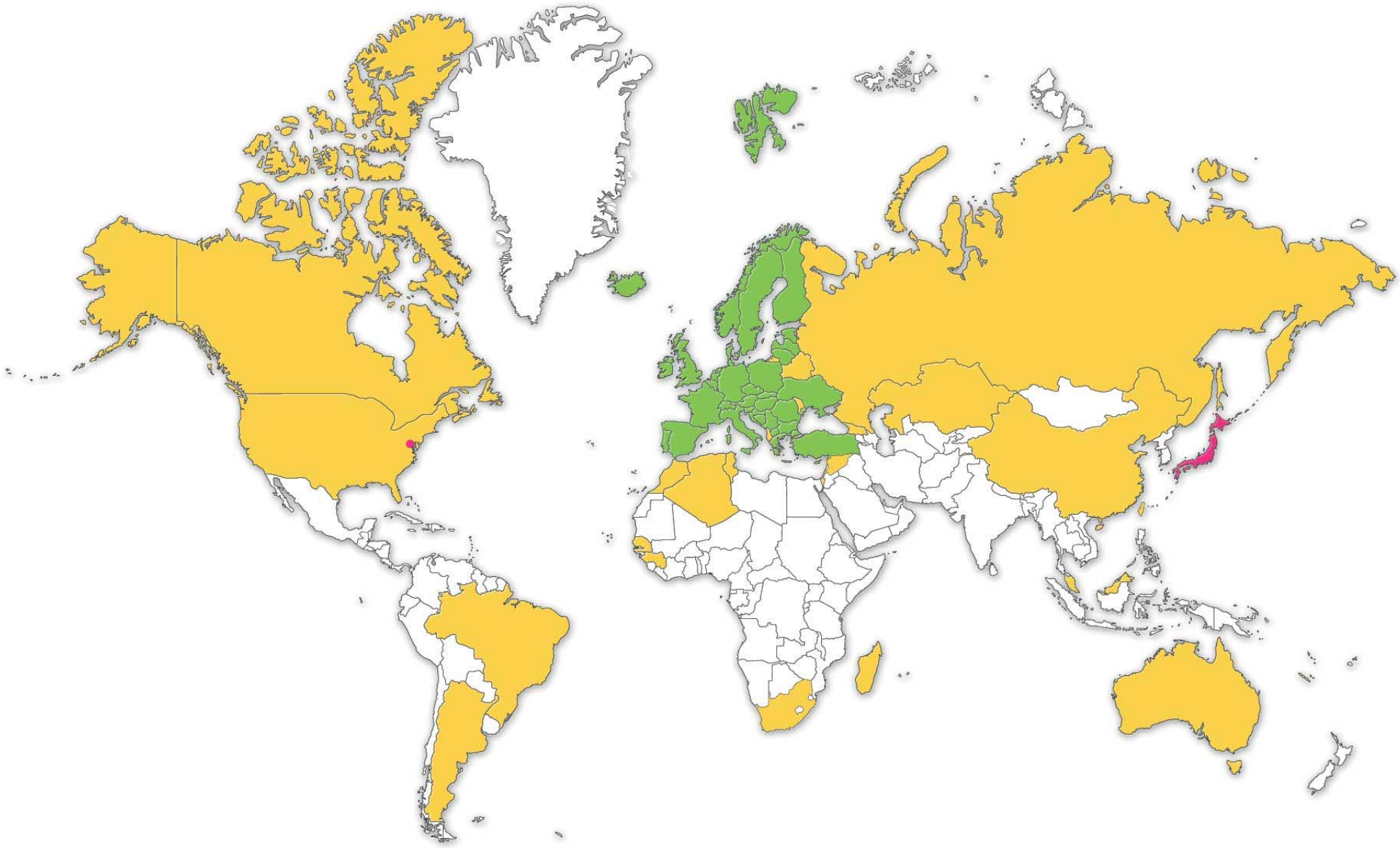
edqm European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

European Directorate for the Quality of Medicines & HealthCare

- The EDQM (European Directorate for the Quality of Medicines & HealthCare) is a directorate of the Council of Europe
- It was founded in 1964 as a partial agreement with the signing of the **Convention on the Elaboration of a European Pharmacopoeia**
- Mission: to contribute to a basic human right: access to good quality medicines and healthcare

Member States and Observers



European Pharmacopoeia & Its Legal Status

- Ph. Eur. is the official Pharmacopoeia, common to all member states – national pharmacopoeias to cover additional subjects of solely national interest
- Lays down common, compulsory standards with the same date of implementation in 37 Ph. Eur. member states
- standards for ALL medicinal products, i.e. ingredients, preparations, dosage forms, containers must comply with the Ph. Eur. requirements when they exist

Some of the EDQM's activities

- European Pharmacopoeia (Ph. Eur.)
- Standard Terms
- Official Medicines Control Laboratories network
- Blood transfusion
- Organ, tissue and cell transplantation
- Anti-counterfeiting activities: Testing activities, Inspection activities, Multisectorial training, Medicrime (CoE)
- Cosmetics and food packaging
- Pharmaceutical care

EDQM and IDMP

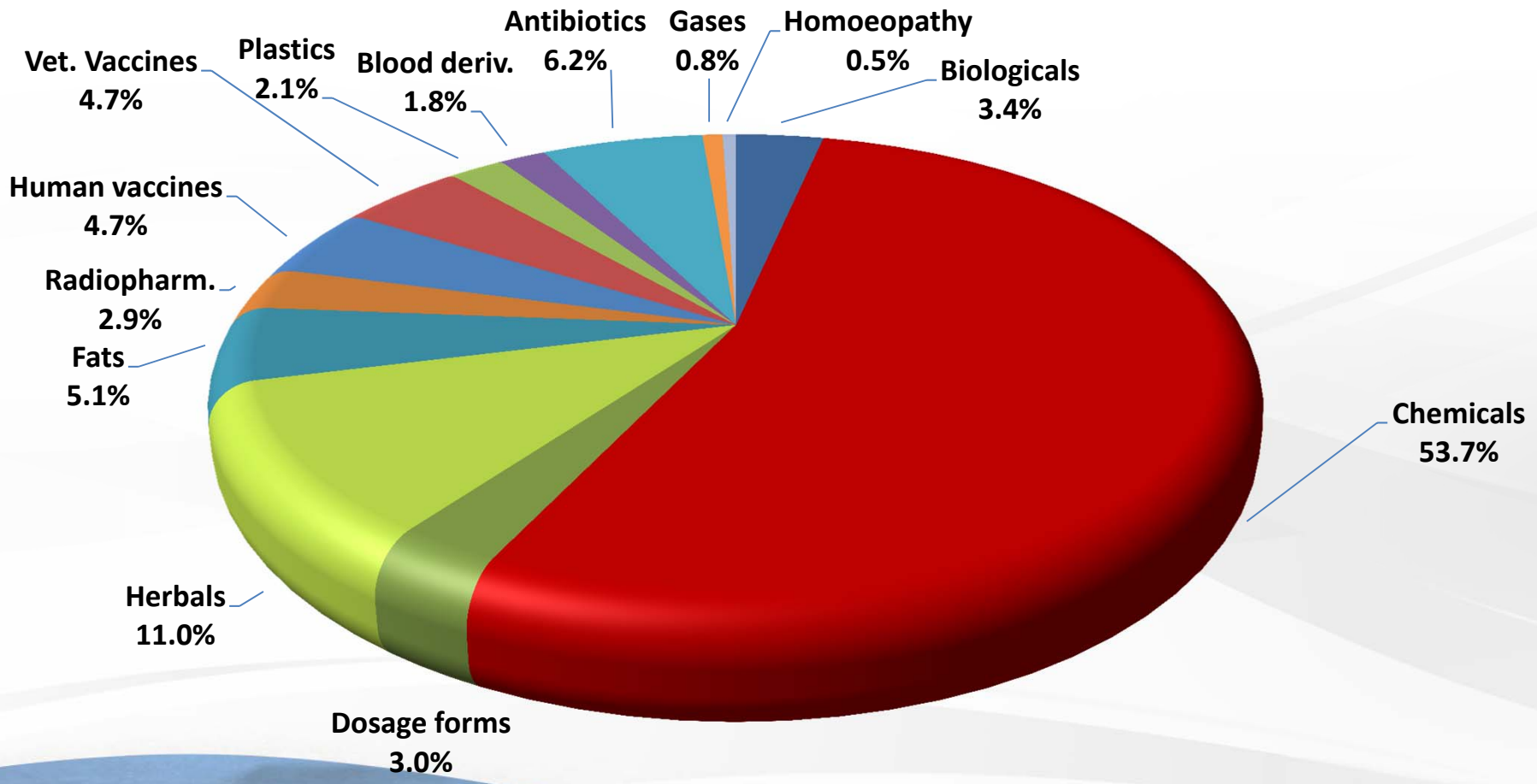
- The EDQM became involved in the IDMP project due to its history of providing standards for medicinal products throughout Europe
  - **European Pharmacopoeia (Ph. Eur.)**
    - Provides quality standards for substances used in medicinal products throughout Europe
  - **Standard Terms → ISO 11239**
    - Provides standardised terminology for use in labelling, packaging, and identification of medicines in 32 world languages
      - dosage forms, routes of administration, packaging

EDQM and GInAS

- The GInAS project is recognised as an extremely important tool for harmonising the identification of substances used in medicinal products

- Information contained in the monographs of the European Pharmacopoeia (Ph. Eur.) is mandated by legislation in the regulation of medicinal products in Europe, and therefore has a natural link with GInAS

Contents of the European Pharmacopoeia:
More than 2200 Monographs and 330 General chapters



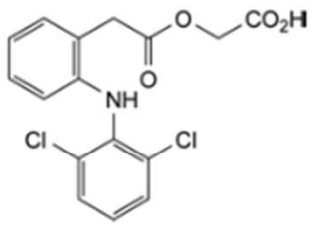
Ph. Eur. identifying information

- Monograph title (English, French, Latin)

07/2009:1281
corrected 7.7

ACECLOFENAC

Aceclofenacum



$C_{16}H_{13}Cl_2NO_4$ M_r 354.2
[89796-99-6]

DEFINITION

[[[2-[(2,6-Dichlorophenyl)amino]phenyl]acetyl]oxy]acetic acid.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: *B*.

Second identification: *A*, *C*.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 50.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 50.0 mL with *methanol R*.

Spectral range: 220-370 nm.

Absorption maximum: at 275 nm.

Reference solution (e). Mix 1.0 mL of reference solution (b) and 1.0 mL of reference solution (d) and dilute to 100.0 mL with the solvent mixture.

Reference solution (f). Dissolve the contents of a vial of *diclofenac impurity A CRS* (aceclofenac impurity I) in 1.0 mL of the solvent mixture, add 1.5 mL of the solvent mixture and mix.

Reference solution (g). Dissolve 4 mg of *aceclofenac for peak identification CRS* (containing impurities B, C, D, E and G) in 2.0 mL of the solvent mixture.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent;
- *temperature*: 40 °C.

Mobile phase:

- *mobile phase A*: 1.12 g/L solution of *phosphoric acid R* adjusted to pH 7.0 with a 42 g/L solution of *sodium hydroxide R*;
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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	70 → 50	30 → 50
25 - 30	50 → 20	50 → 80
30 - 50	20	80

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 275 nm.

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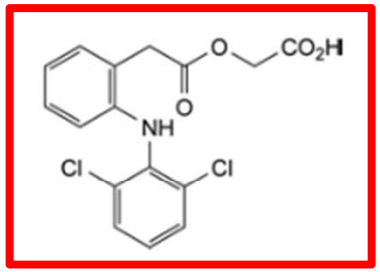

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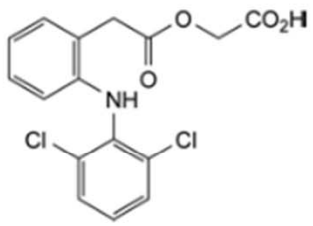

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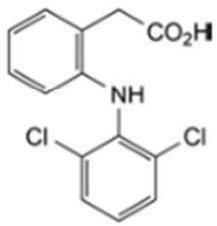
  - Description of more complex substances
- Graphical formula and nomenclature of impurities

STORAGE

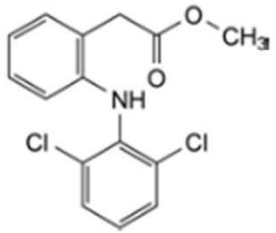
Protected from light.

IMPURITIES

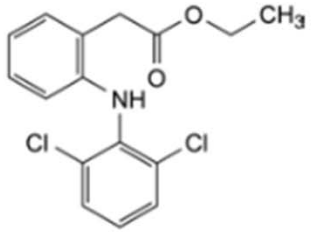
Specified impurities: A, B, C, D, E, F, G, H, I.



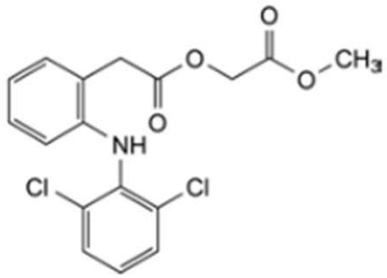
A. [2-[(2,6-dichlorophenyl)amino]phenyl]acetic acid (diclofenac),



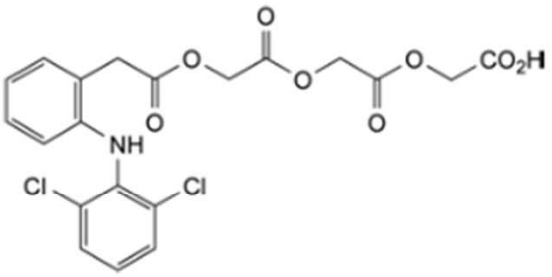
B. methyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (methyl ester of diclofenac),



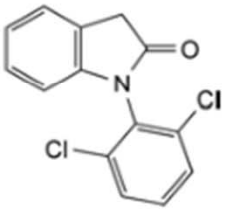
C. ethyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (ethyl ester of diclofenac),



G. [[[[[2-[(2,6-dichlorophenyl)amino]phenyl]-acetyl]oxy]acetyl]oxy]acetic acid (acetic aceclofenac),



H. [[[[[[[2-[(2,6-dichlorophenyl)amino]phenyl]-acetyl]oxy]acetyl]oxy]acetyl]oxy]acetic acid (diacetic aceclofenac),

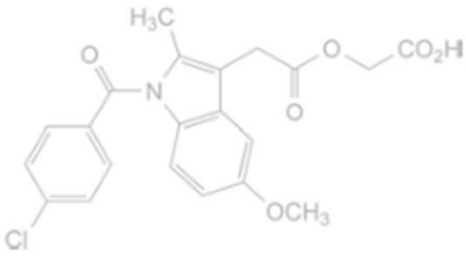


I. 1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one.

04/2008:1686
corrected 7.0

ACEMETACIN

Acemetacinum



$C_{21}H_{18}ClNO_6$ M_r 415.8

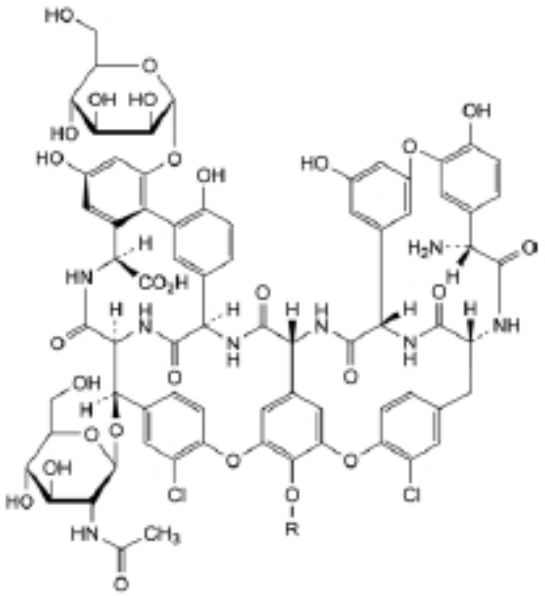
[53164-05-9]

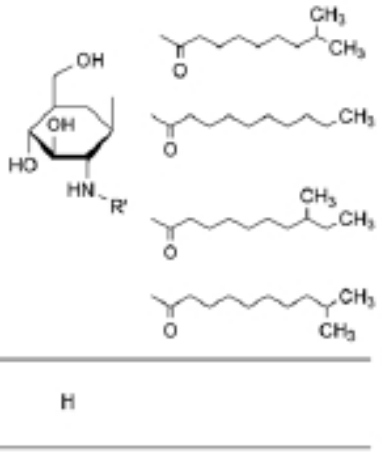
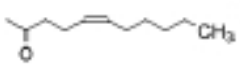
DEFINITION

01/2009:2358
corrected 6.6

TEICOPLANIN

Teicoplaninum



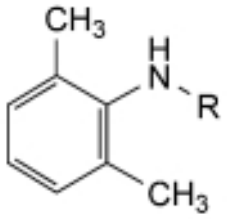
Teicoplanin	R	R'
A_{2-1} $C_{88}H_{96}Cl_2N_9O_{33}$ M. W.: 1878		
A_{2-2} $C_{88}H_{97}Cl_2N_9O_{33}$ M. W.: 1880		
A_{2-3} $C_{88}H_{97}Cl_2N_9O_{33}$ M. W.: 1880		
A_{2-4} $C_{89}H_{99}Cl_2N_9O_{33}$ M. W.: 1894		
A_{2-5} $C_{89}H_{99}Cl_2N_9O_{33}$ M. W.: 1894		
A_{3-1} $C_{72}H_{68}Cl_2N_9O_{28}$ M. W.: 1564	H	

DEFINITION

Mixture of glycopeptides produced by certain strains of *Actinoplanes teichomyceticus sp.*; the 6 principal components of the mixture are teicoplanin A_{2-1} to A_{2-5} and teicoplanin A_{3-1}.

The Markush « Problem » at the level of the « main » substance (exceptional)

The Markush « Problem » in the impurities section (often)



A. R = H: 2,6-dimethylaniline,

C. R = CO-CH_3: *N*-(2,6-dimethylphenyl)acetamide,

D. R = CO-CH_2-NH-C_2H_5: *N*-(2,6-dimethylphenyl)-2-(ethylamino)acetamide,

G. R = CO-CH_2-NH-$CH(CH_3)_2$: *N*-(2,6-dimethylphenyl)-2-[(1-methylethyl)amino]acetamide,

H. R = CO-CH_2-Cl: 2-chloro-*N*-(2,6-dimethylphenyl)acetamide,

K. R=CO-CH_2-N(CH_3)C_2H_5: *N*-(2,6-dimethylphenyl)-2-(ethylmethylamino)acetamide,

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  - Description of more complex substances
- Graphical formula and nomenclature of impurities
- Information about polymorphic form (existence or specifically defined)

DEFINITION

Pentazocine contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (2*RS*,6*RS*,11*RS*)-6,11-dimethyl-3-(3-methylbut-2-enyl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ol, calculated with reference to the dried substance.

CHARACTERS

A white or almost white powder, practically insoluble in water, freely soluble in methylene chloride and soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the *Ph. Eur. reference spectrum for pentazocine (form A)*.

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- Production

ARNICA TINCTURE

Arnicae tinctura

DEFINITION

Tincture produced from *Arnica flower (1391)*.

Content: minimum 0.04 per cent of sesquiterpene lactones expressed as dihydrohelenalin tiglate ($C_{20}H_{26}O_5$; M_r 346.42).

PRODUCTION

The tincture is produced from the herbal drug by a suitable procedure using 10 parts of ethanol (60-70 per cent *V/V*) for 1 part of drug.

Additional information in the Knowledge database

- Each monograph also has an entry in the freely accessible EDQM Knowledge database
- Further information is available for each substance, for example:
  - official Ph. Eur. reference standards
  - certificate holders
  - monograph revision history
  - chromatograms

https://extranet.edqm.eu/4DLink1/4DCGI/Web_View/mono/1281

How could potentially EDQM and « GInAS » collaborate?

Exchange/synchronisation of

- Chemical structures for the main compounds
- Chemical structures for the impurities (Attention: Markush structures)
- Names
- Nomenclature
- Definition
- Production information
- Special grades
- Sample Chromatograms

Summary

- The EDQM has actively supported the IDMP project since its early years, in ISO and in ICH, providing the principal editor for the ISO 11239 standard and implementation guide
- The EDQM and the European Pharmacopoeia is looking forward to working with GInAS to find the best way to share relevant substance information in an efficient, maintainable way

Thank you!

www.coe.int

www.edqm.eu

pharmeuropa.edqm.eu

standardterms.edqm.eu

European Directorate for the Quality of Medicines & HealthCare (EDQM)
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