Specific monographs: a guide through the different sections

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Dr Ulrich Rose
Head of Division
European Pharmacopoeia Department
EDQM

Basis for the elaboration of monographs

SAFETY FIRST!

Products of proven safety, evaluated and approved by competent authorities of Member states

Impurity profiles for existing, approved manufacturing routes

Use of robust, validated analytical methods

Specific monographs

APIs, excipients, finished products

COMPLEMENTARITY

Specific monographs
Finished products (FP)

- ***Vaccines and sera***
- ***Blood products***
- ***Radiopharmaceuticals***
- ***Insulin preparations***

New approach (March 2014)

Monographs on finished products with chemically-defined APIs

Sitagliptin tablets (2927)

Raltegravir tablets (2938)

Raltegravir chewable tablets (2939)

Specific monographs

- Title
- Relative atomic and molecular masses
- CAS registry number

- Definition
- Production (mandatory for manufacturer)

- Potential adulteration (information may be available)
- Characters (for information only)

Specific monographs

- Identification
- Tests
- Assay

- Storage (information and recommendation, but competent authority may make it mandatory)
- Labelling

- Impurities - transparency list
- Functionality - related characteristics (not mandatory)
  → Excipients monographs

01/2017:1002

Version date

DICLOFENAC SODIUM

English (or French) **title**

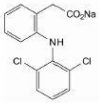
Diclofenacum natricum

Latin subtitle

- **Molecular and graphic formulae**

- **Relative atomic or molecular mass**

- **CAS number**



$C_{14}H_{10}Cl_2NNaO_2$ M_r 318.1

[15307-79-6]

Official definition

DEFINITION

Sodium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate.

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

Characters

Section for information e.g. appearance, solubility

CHARACTERS

Appearance: white or slightly yellowish, slightly hygroscopic, crystalline powder.

Solubility: sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), slightly soluble in acetone.

mp: about 280 °C, with decomposition.

Reference standard available from EDQM (*diclofenac sodium CRS*)

Identification tests

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *diclofenac sodium CRS*.

B. Thin-layer chromatography (*2.2.27*).
Test solution. Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.
Reference solution (a). Dissolve 25 mg of *diclofenac sodium CRS* in *methanol R* and dilute to 5 mL with the same solvent.
Reference solution (b). Dissolve 10 mg of *indometacin R* in reference solution (a) and dilute to 2 mL with reference solution (a).

Further information provided on Knowledge database

(http://www.edqm.eu/en/Knowledge-Database-707.html)

Plate: *TLC silica gel GF_{254} plate R*.
Mobile phase: *concentrated ammonia R, methanol R, ethyl acetate R* (10:10:80 *V/V/V*).
Application: 5 µL.
Development: over 1/2 of the plate.
Drying: in air.
Detection: examine in ultraviolet light at 254 nm.
System suitability: reference solution (b):
– the chromatogram shows 2 clearly separated spots.
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).

C. Dissolve about 10 mg in 10 mL of *ethanol (96 per cent) R*. To 1 mL of this solution add 0.2 mL of a mixture, prepared immediately before use, of equal volumes of a 6 g/L solution of *potassium ferricyanide R* and a 9 g/L solution of *ferric chloride R*. Allow to stand protected from light for 5 min. Add 3 mL of a 10 g/L solution of *hydrochloric acid R*. Allow to stand, protected from light, for 15 min. A blue colour develops and a precipitate is formed.

D. Dissolve 60 mg in 0.5 mL of *methanol R* and add 0.5 mL of *water R*. The solution gives reaction (b) of sodium (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and its absorbance (*2.2.25*) at 440 nm is not greater than 0.05.

Dissolve 1.25 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

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

Reference solution (a). Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve the contents of a vial of *diclofenac for system suitability CRS* (containing impurities A and F) in 1.0 mL of the mobile phase.

Column:
– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 34 volumes of a solution containing 6.5 g/L of *phosphoric acid R* and 0.8 g/L of *sodium dihydrogen phosphate R*, previously adjusted to pH 2.5 with *phosphoric acid R*, and 66 volumes of *methanol R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL.

Run time: 1.6 times the retention time of diclofenac.

Identification of impurities: use the chromatogram supplied with *diclofenac for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and F.

Relative retention with reference to diclofenac (retention time = about 25 min): impurity A = about 0.4; impurity F = about 0.8.

System suitability: reference solution (b):
– *resolution*: minimum 4.0 between the peaks due to impurity F and diclofenac.

Calculation of percentage contents:
– *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity F = 0.3;
– for each impurity, use the concentration of diclofenac in reference solution (a).

Limits:
– *impurity A*: maximum 0.2 per cent;
– *impurity F*: maximum 0.15 per cent;
– *unspecified impurities*: for each impurity, maximum 0.10 per cent;
– *total*: maximum 0.4 per cent;
– *reporting threshold*: 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 for 3 h.

ASSAY

Dissolve 0.250 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 31.81 mg of $C_{14}H_{10}Cl_2NNaO_2$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities: A, F.

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*): B, C, D, E.

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

B. 2-[(2,6-dichlorophenyl)amino]benzaldehyde,

C. [2-[(2,6-dichlorophenyl)amino]phenyl]methanol,

D. [2-[(2-bromo-6-chlorophenyl)amino]phenyl]acetic acid,

E. 1,3-dihydro-2*H*-indol-2-one,

Reference to general Chapters: 2.2.29

Reagent described in the Ph.Eur.: ***phosphoric acid R***

Transparency list

TITLE

DICLOFENAC SODIUM

Diclofenacum natricum

- INNs used almost universally
  (modified to indicate salt)
- Includes degree of hydration
  - «*x* hydrate»: if well-defined form (*x* = hemi, mono, di, tri, tetra, etc.)
  - «hydrate»: if a mixture of hydrates

DEFINITION (1)

DEFINITION (DICLOFENAC SODIUM)
Sodium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate.
Content: 99.0 per cent to 101.0 per cent (dried substance).

- Chemical nomenclature
- Assay limits
  - Content expressed on anhydrous or dried basis
  - Solvent-free substance is implied, even where not stated
    (see *Substances for Pharmaceutical Use, Residual solvents*)

- LC assay: reflect assay variability and purity
  (e.g.: 96.0-102.0 % means 2 % assay variability and 2.0 % total impurities)
- Volumetric titration: usually 99.0 to 101.0 %
- Microbiological assay: minimum activity (IU/mg, as is)
- Biological assay: specific activity (e.g.: IU/mg)

DEFINITION (2)

- Statements on scope (e.g. route of synthesis, degree of hydration):
  - A well-defined hydrate (mono, di, tri, etc.): no specific statement, cf. chemical nomenclature (meldonium dihydrate, caffeine monohydrate)
  - A mixture of different hydrate forms ("$x H_2 0$"): "It contains a variable quantity of water" (zanamavir hydrate, thiocolchicoside hydrate, valaciclovir hydrochloride hydrate)
  - Water- free **and** hydrate form: "It may be anhydrous or contain a variable quantity of water" (fluvastatin sodium, saccharin sodium)
- Monograph applies to all grades, unless otherwise stated
- Special grades may be mentioned in body of monograph (parenteral etc.): pethidine hydrochloride, fructose

PRODUCTION

PRODUCTION

Dalteparin sodium is produced by a validated manufacturing and purification procedure under conditions designed to minimise the presence of N-NO groups.

The manufacturing procedure must have been shown to reduce any contamination by N-NO groups to approved limits using an appropriate, validated quantification method.

Instructions for manufacturers

Source materials, manufacturing process, validation, control, in-process testing

Cannot necessarily be verified by independent analyst

Compliance established by competent authorities

→ e. g. genotoxic impurities

CHARACTERS

CHARACTERS (DICLOFENAC SODIUM)
Appearance: white or slightly yellowish, slightly hygroscopic, crystalline powder.
Solubility: sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), slightly soluble in acetone.
mp: about 280 °C, with decomposition

- No analytical requirement
- Useful information for the analyst

- Polymorphism, where known, is mentioned (cf *5.9 Polymorphism*)
- Physical properties may be mentioned (melting point, density)
- See also chapter 5.11: Characters section in monographs
  (methods to determine hygroscopicity, crystallinity, solubility)

IDENTIFICATION

- First and Second identifications → defined in General Notices
- Sometimes cross-reference to "Tests"
- Reference to Water/ Loss on drying (applicable for a hydrate)

1st identification alone → always sufficient
2nd identification → never mandatory

2nd identification →usually less sophisticated; may be performed in pharmacies e.g. TLC, wet chemical reaction

IDENTIFICATION
First identification: A, D.
Second identification: B, C, D.
A. Infrared absorption spectrophotometry (2.2.24).
Comparison: diclofenac sodium CRS.

B. Thin-layer chromatography (2.2.27).
Test solution. Dissolve 25 mg of the substance to be examined in methanol R and dilute to 5 mL with the same solvent.
Reference solution (a). Dissolve 25 mg of diclofenac sodium CRS in methanol R and dilute to 5 mL with the same solvent.
Reference solution (b). Dissolve 10 mg of indometacin R in reference solution (a) and dilute to 2 mL with reference solution (a).
Plate: TLC silica gel GF_{254} plate R.
Mobile phase: concentrated ammonia R, methanol R, ethyl acetate R (10:10:80 *V/V/V*).
Application: 5 µL.
Development: over 1/2 of the plate.
Drying: in air.
Detection: examine in ultraviolet light at 254 nm.
System suitability: reference solution (b):
– the chromatogram shows 2 clearly separated spots.
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).

C. Dissolve about 10 mg in 10 mL of ethanol (96 per cent) R. To 1 mL of this solution add 0.2 mL of a mixture, prepared immediately before use, of equal volumes of a 6 g/L solution of potassium ferricyanide R and a 9 g/L solution of ferric chloride R. Allow to stand protected from light for 5 min. Add 3 mL of a 10 g/L solution of hydrochloric acid R. Allow to stand, protected from light, for 15 min. A blue colour develops and a precipitate is formed.

D. Dissolve 60 mg in 0.5 mL of methanol R and add 0.5 mL of water R. The solution gives reaction (b) of sodium (2.3.1).

TESTS

Chemical methods

Physical methods

Chromatographic methods

Organic impurities

Inorganic impurities

Volatile impurities

Impurity testing (in line with ICH Q3A/B) (1)

Specified impurities

- detected, identified by SST/ peak identification CRS
- individual acceptance criteria

Unspecified impurities ("ODIs")

- impurity is detected, but not individually identified
- limit for "unspecified impurities" (or *Substances for Pharmaceutical Use*)

Knowledge database

Status	In Use
Monograph Number	02780
English Name	Temozolomide
French Name	Témozolomide
Latin Name	Temozolomidum
Pinyin Name	
Chinese Name	
Pharmeuropa	29.3
Published in English Supplement	9.4
Published in French Supplement	9.4
Chromatogram	Available
Additional information	Not available
History	View history
Interchangeable (ICH_Q4B)	NO
International Harmonisation chapter 5.8	NO

Reference standards

Available since	Cat. No.	Name	Batch No.	Unit Quantity	Price	SDS Product Code
	Y0001827	Temozolomide	1	70 mg	79 EUR	201601104
	Y0001960	Temozolomide for peak identification	1	10 mg	79 EUR	201601104

Practical Information

Test(s)	Brand Name/Information
Related substances and assay	Luna C18, Luna C18 (2); Inertsil ODS3 and ODS4 are NOT suitable
Water	anhydrous methanol and Hydranal coulomat AG

- Aim of the revision
- State of work, history, chromatograms

- Reference standards (CRS)
- Trade names (column, reagents...)

Impurity testing (2): Impurities section

Not necessarily exhaustive

Impurities **known** to be detected by mono tests

Usually controlled by related substances test, but may be other tests, e. g. UV absorbance ratio

Based on information obtained and verified during monograph elaboration/ revision

DACARBAZINE

IMPURITIES

Specified impurities: *A*, *B*, *D*.

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*): *C*.

A. 3,7-dihydro-4*H*-imidazo[4,5-*d*]-1,2,3-triazin-4-one (2-azahypoxanthine),

B. X = H_2: 5-amino-1*H*-imidazole-4-carboxamide,

C. X = NH: 5-diazenyl-1*H*-imidazole-4-carboxamide,

D. *N*-methylmethanamine.

Inorganic impurities

- Result from the manufacturing process or from raw materials
- Known and identified:
  - Reagents, ligands catalysts
  - Elemental impurities → ICH Q3D Guideline for Elemental impurities
  - Inorganic salts
  - Other materials (e.g. filter aids)
- Atomic absorption spectrometry (*2.2.23) or other techniques*
- Sulfated ash (*2.4.14*): global determination of foreign cations

Residual solvents

- Specific monographs do not include a test for residual solvents, *except*:
  - **Class 1** solvents are always named and limited in monographs

    Ethambutol hydrochloride (0553): Impurity D (1,2-dichloroethane): maximum 5 ppm
  - **Class 2** solvents: not included in a specific monograph; limit set by option 2 (cf. 5.4 Residual solvents)
  - **Class 3** solvents are only named and limited in monographs when they exceed 0.5% (impact on assay results)

    Olmesartan medoxomil (2600): Acetone: maximum 0.6 per cent

ASSAY

ASSAY (DICLOFENAC SODIUM)

Dissolve 0.250 g in ▶60◀ mL of anhydrous acetic acid R. Titrate with 0.1 M perchloric acid, determining the end-point potentiometrically (2.2.20).

1 mL of 0.1 M perchloric acid is equivalent to 31.81 mg of $C_{14}H_{10}Cl_2NNaO_2$.

Often physico-chemical assay methods, but also bio/immuno and microbiological assays

Unspecific but precise assay (titration),

provided sufficiently characteristic and selective related substances test (cf Technical guide)

Chromatographic assays:

assay standards + repeatability requirements (cf. general chapter 2.2.46)

STORAGE

STORAGE (DICLOFENAC SODIUM)

In an airtight container, protected from light.

Not mandatory section

→

Competent authority may specify particular storage conditions

→ may decide to make it mandatory

Storage of the product

→ to ensure compliance with the monographs

Conventional expressions

→ defined in the General Notices

(e. g. *in an airtight container, protected from light)*

LABELLING

SORBITOL

LABELLING

The label states:

- where applicable, the maximum concentration of bacterial endotoxins,
- where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

Covered by national and international regulations

Information provided with the product included in “labelling”:

package, leaflet, certificate of analysis

Labelling items needed for the application of monographs,

e.g. nominal values (especially excipients)

Informational items or recommendations included

FUNCTIONALITY-RELATED CHARACTERISTICS (FRCs)

Described in monographs on Excipients

Section is not mandatory

Provides information on important parameters

→ Chapter on FRCs 5.15

Tests are linked to use

(lubricant, tablet compression, etc.)

SORBITOL

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sorbitol used as filler and binder in tablets.

CONCLUSION

- Complementarity of specific and general monographs/chapters
- New: Monographs on finished products with chemically-defined APIs (e. g. sitagliptin tablets)
- Not mandatory sections: Characters, Storage, FRC
- Other sections
  - In general mandatory
  - Production (mandatory for manufacturer)
- Knowledge database: SOW, reference standards, CEP-holders, trade names

Thank you for your attention!