Federal Institute for Medicinal Products and Medical Devices

Announcement of a communication on the German Pharmacopoeia (recommendations of the specialised committees of the German Pharmacopoeia Commission)

From 3 April 2019

On the basis of Section 7(5) of the Rules of Procedure for the German Pharmacopoeia Commission and its bodies of 17 July 2009 (notice of 8 October 2009, BfArM website), recommendations of the specialist committees of the German Pharmacopoeia Commission are the professional and business circles.

The Pharmaceutical Biology Committee has recommended a draft of a new monogra phie for inclusion in the DAB (annex).

New monograph

Discontinued cannabis extract (Cannabis extractum normatum)

The draft is hereby made public.

Comments on the drafts for the German Pharmacopoeia must be sent by 1 July 2019 at the latest, including to the office of the Pharmacopoeia Commissions at the Federal Institute for Medicinal Products and Medical Devices, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, to direct.

Bonn, 3 April 2019 65.1.02-3660-7412-8631/19

Federal Institute for Medicinal Products and Medical Devices

Representing Knöss

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Notice

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Discontinued cannabis extract Cannabis extractum normatum

Definition

The extract produced and adjusted from the whole or crushed, flowering, dried shoot tips of the female plants of Cannabis sativa L. (Cannabaceae).

Assay:

- ^{9}-tetrahydrocannabinol (C H O ; M 314.5): at least 1% and not more than 25% (m/m) for the extract and $_{21302\ r}$

90 to 110 percent of the nominal assay indicated in the label

– Cannabidiol ($C_{21}H_{30}O_2$; M_r 314.5): not more than 10 % (m/m) for the extract and 90 to 110 % of the nominal content specified in the restriction

Manufacture

The extract is produced by a suitable extraction method such as a heptane, ethanol or CO_2extraction. The obtained raw extract is optionally refined, dissolved in a suitable fatty oil as in medium chain triglycerides, grape seed oil or similar, and thus adjusted to the indicated content.

The cannabinoid acids are decarboxylated, in a suitable place during manufacture.

Properties

Appearance: yellow to brown liquid.The extracts dissolved in a suitable fatty oil have characteristic relative densities and refractive indices.Checking for identity
The test is carried out using high-performance thin-film chromatography (2.8.25).

Investigation solution: (0.5 mg/ml THC or CBD) The weighing of the preparation must be adjusted taking into account the given main cannabinoids. The corresponding weigh-in is supplemented with a suitable solvent (e.g. 2-propanol R or methanol R)to 10.0 ml. The solution is then filtered through a membrane filter of 0.45 micronnominal pore width. This solution serves as an investigation solution.

Reference solution a: 5 mg cannabidiol RN and 5 mg x^{9}-tetrahydrocannabinol RN are dissolvedin 10.0 ml of methanol R. Reference solution b:2.5 ml reference solution a are mixed with methanolRdiluted to 10.0 ml (intensity marker IM).Reference solution c:5 mg cannabinolRNand 5 mg cannabidiolRNin 10.0 ml of methanol.Rsolved.Intensity markers:•^{9}tetrahydrocannabinol.

Stationary phase: DC plate with octadecylylated silica gel F_{254} R (2 to 10 microns).Applying:5Ul; band-shaped 8 mm.

Flow agent: Mixture of 15 volume parts acetic acid 99 % R,15 volume parts water R and 70 volume parts methanol R.

Running distance: 60 mm

detection and evaluation: The plate is dried in the air, then sprayedwith vanillin reagent R and

heated for about 15 min at 100 to 105 °C. The evaluation takes place in daylight.

Aptitude test: Reference solution cThe chromatogram must show 2 clear zones in the lower third. The lower zone (cannabinol) is light-violet, the upper zone (cannabidiol) is purple.

Result: The zone sequence in the chromatograms of reference solution a and examination solution is shown in the following information. Further weak to very weak purple zones may be present in the chromatogram of the examination solution.

Discontinued cannabis extract

Upper plate edge

CBD: purple zone

CBN: light-violet zone -9-THC: violet zone

violet zone (CBD)

violet zone (. . . . . .

Plant

Reference solution

Investigation solution

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Testing for purityCannabinol: Up to 1.0 percent. The test is carried out using liquid chromatography (2.2.29) as

Determination of content, using the reference solution III.The percentage of cannabinol ($C_{21}H_{26}O_2$) is calculated according to the followingformula: content=F_u G_r .d/F_r .e_u .100inmg^{-1} $C_{21}H_{26}O_2$. F_u = peak area of cannabinol in the chromatogram of the examination solution.e_r = weigh-in cannabinol in milligram.G_r = content cannabinol in percent.F_r = peak area of the Cannabinol in the chromatogram of the reference solution III.e_u = weighing preparation in grams.d = relative density in g x cm^{-3}.
Water (2.5.12):maximum 0.5 percent, with 0.200 g of substance.Assay determination
The test is carried out using liquid chromatography (2.2.29)

Examination solution: (0.2 mg/ml THC or CBD) The weighing of the preparation must be adjusted taking into account the given main cannabinoids. The corresponding weigh-in is supplemented with ethanol 96% R to 25.0 ml. The solution is used as an examination solution after filtration by a membrane filter made of regenerated cellulose of 0.20 micronnominal nominal pore width.

Reference solution I: 5.0 mg x^9-tetrahydrocannabinol RN are dissolved in methanol R to 25.0 ml. The calibration solution has a concentration of 0.200 mg ml^{-1}.

Reference solution II: 5.0 mg cannabidiol RN are dissolved in methanol R to 25.0 ml. The calibration solution has a concentration of 0.200 mg ml^{-1}.

Reference solution III: 5.0 mg cannabinol RN are dissolved in methanol R to 25.0 ml (stock solution). From this solution, by diluting with methanol R, a calibration solution with the concentration of 0.002 mg $ml^{-1.}$

Reference solution IV: 5.0 mg x^8-Tetrahydrocannabinol RN are dissolved in methanol R to 25.0 ml. 1.0 ml solution is mixed with 1.0 ml of the reference solution I and supplemented with methanol R to 10.0 ml.

Chromatography can be performed as follows:

Pre-pillar

– Size:l=5mm,diameter=3.0mm
- Stationary phase: octadecylylated silica gel for chromatography R (2.7 microns)

Pillar

- - Size:l=0.15m,x=3.0mm
- – Stationary phase: octadecylylated silica gel for chromatography R (2.7 microns)

  Poroshell 120 EC-C18 - Column Agilent

- - Temperature: 40 °C

  Elution

  Mobile phase: A: aqueous solution of phosphoric acid 85% R (8.64 g) L^{-1}) Mobile Phase B: Acetonitrile RFlow rate: 1.0 ml . . . . . .

Mobile Phase A [% V/V]	Mobile Phase B [% V/V]

Time [min]

0 - 16 16 - 17 17 - 20

Investigation conditions

36 x 18 18 x 36 36

64 x 82 82 x 64 64

Explanations

linear gradient linear gradient equilibration

Detection: Spectrometer at 225 nm
disassembly system: sample loopinjection
volume: 10 ul; Investigation solution, reference solution Recording time: 20 min

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Relative retention (relative to tetrahydrocannabinol, t_R about 8.7 min)

- ^{8}-Tetrahydrocannabinol:

- Cannabidiol:

- Cannabinol:

Aptitude test

about 1.04 about 0.58 about 0.83

Resolution: At least 1.5 between the peaks of tetrahydrocannabinol and .8-tetrahydrocannabinol in chro-

matogram of the reference solution IV.

Precision: The reference solutions I and II are injected 6 times and the surfaces of the tetrahydrocannabinol and cannabidiol corresponding peaks are determined.

The test may only be evaluated if the relative standard deviation of the individual values from the mean is not more than 1.0 percent.

Evaluation

A. The percentage oftetrahydrocannabinol ($C_{21}H_{30}O_2$)is calculated according to the following formula: content=$F_{u\text{-}a}$ $e_{r\text{-}a}$ $G_{r\text{-}a}$ d/$F_{r\text{-}a}$ u100inmg ml^{-1} $C_{21}H_{30}O_2$. $F_{u\text{-}a}$ = peak area of the tetrahydrocannabinol in the chromatogram of the examination solution.$e_{r\text{-}a}$ = weight of^{9}-tetrahydrocannabinol in milligrams.

$G_{r\text{-}a}$ = tetrahydrocannabinol in percentage.$F_{r\text{-}a}$ = peak area of the tetrahydrocannabinolin the chromatogram of the reference solution I.e_u = weighing Preparation in grams.d = relative density in g cm^{-3}.B. The percentage of cannabidiol ($C_{21}H_{30}O_2$) is calculated according to the followingformula: Content=$F_{u\text{-}b}$ $G_{r\text{-}b}$ d/$F_{r\text{-}b}$ u100inmg ml^{-1} $C_{21}H_{30}O_2$. $F_{u\text{-}b}$ = peak area of cannabidiol in the chromatogram of the examination solution.$e_{r\text{-}b}$ = weigh-in cannabidiol in milligram.$G_{r\text{-}b}$ = content cannabidiol in percent.$F_{r\text{-}b}$ = Peak area of cannabidiol in the chromatogram of the reference solution II.e_u = weighing preparation in grams.d = relative density in g x cm^{-3}.

Storage

Tightly closed, protected from light, at 2 to 8 °C.

Labeling

The calculated percentage of•^{9}-tetrahydrocannabinol and cannabidiol shall be indicated on the container. Stabilisers shall be indicated by type and quantity.