

Novel Polymorphic Form of Rotigotine and Process for Production

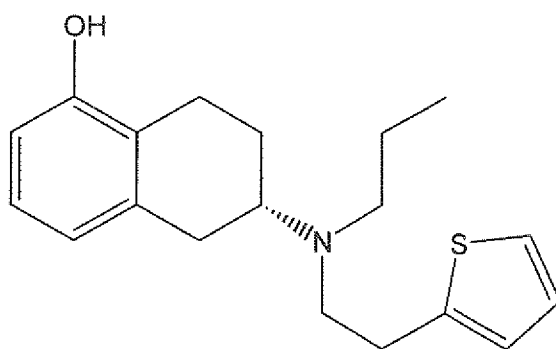
5	Description
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Field of the Invention

The present invention relates to a novel polymorphic form
10 (form II) of Rotigotine and a process for production thereof,
which form is useful for the manufacture of a stable
medicament for treating or alleviating symptoms of
Parkinson's Disease and other dopamine-related disorders.

15 Technical Background

Rotigotine is the International Non-Proprietary Name (INN) of the compound (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol having the structure shown below



25 Rotigotine is a non-ergolinic D1/D2/D3 dopamine agonist that resembles dopamine structurally and has a similar receptor profile but a higher receptor affinity.

In contrast to other non-ergolinic dopamine agonists, Rotigotine has significant D1 activity, which may contribute to a greater physiological action.

- 5 In contrast to ergolinic compounds, Rotigotine has a very low affinity for 5 HT_{2B} receptors and thus a low risk of inducing fibrosis.

10 Actions on non-dopaminergic receptors (such as 5-HT_{1A} agonism and A_{2B} antagonism) may contribute to other beneficial effects, such as antidyskinetic activity, neuroprotective activity and antidepressive effects.

15 Rotigotine is disclosed as active agent for treating patients suffering from Parkinson's disease (described in WO 2002/089777), Parkinson's plus syndrome (described in WO 2005/092331), depression (described in WO 2005/009424) and the restless-legs syndrome (described in WO 2003/092677) as well as for the treatment or prevention of dopaminergic
20 neuron loss (described in WO 2005/063237).

Known pharmaceutical compositions containing Rotigotine comprise a transdermal therapeutic system (TTS) (described in WO 99/49852), a depot form (described in WO 02/15903), an
25 iontophoretic device (described in WO 2004/050083) and an intranasal formulation (described in WO 2005/063236).

Each of the above cited publications is incorporated by reference in its entirety herein.

30

One crystalline form of Rotigotine is already known and will hereinafter be designated as polymorphic form (I).

35 Surprisingly a further crystalline form of Rotigotine (polymorphic form (II)) has now been identified and found to show a greatly enhanced thermodynamic stability and an improved shelf-life as well as a cubic crystal shape that

represents an advantage over the needle like particles of polymorphic form (I) regarding its handling properties such as filtering properties, flowability, electrostatic behaviour, etc.

5

The discovery of a second crystalline Rotigotine polymorph is especially astonishing as Rotigotine is a commercial drug that has been known since the mid eighties and has been well investigated over the past decade. Furthermore, no indication
10 for the presence of a second crystalline Rotigotine polymorph was observed in a first polymorphism screening that was earlier conducted during formulation development.

Summary of the Invention

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The present invention provides a novel polymorphic form (form II) of Rotigotine ((-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl) ethyl]-amino]-1-naphthalenol).

20 The novel polymorphic form of Rotigotine according to the present invention has at least one of the following characteristics:

a X-ray powder diffraction spectrum comprising a peak at
25 least at one of the following $^{\circ}2\theta$ angles (± 0.2): 12.04, 13.68, 17.72 and/or 19.01, measured with Cu-K $_{\alpha}$ irradiation (1.54060 Å);

a Raman spectrum comprising at least one peak at the
30 following wave numbers ($\pm 3 \text{ cm}^{-1}$): 226.2, 297.0, 363.9, 737.3, 847.3, 1018.7 and/or 1354.3;

a differential scanning calorimetry (DSC) peak with a T_{onset}
at $97^{\circ}\text{C} \pm 2^{\circ}\text{C}$ measured with a heating rate of $10^{\circ}\text{C}/\text{min}$;
35 and/or

a melting point of $97^{\circ}\text{C} \pm 2^{\circ}\text{C}$.

In one embodiment the novel polymorphic form of Rotigotine is characterized by two, three or four of the following X-ray powder diffraction peaks ($^{\circ}2\theta$) (± 0.2): 12.04, 13.68, 17.72, 19.01, measured with a Cu-K $_{\alpha}$ irradiation (1.54060 Å).

In one embodiment the novel polymorphic form of Rotigotine according to the invention is characterized by peaks in its Raman spectrum at the wave numbers 297.0, 847.3 and 1018.7 ± 3 cm $^{-1}$.

The temperatures given herein include variations of $\pm 2^{\circ}\text{C}$ due to measurement inaccuracies, e.g. of a DSC experiment. The $^{\circ}2\theta$ angles given herein include variations of ± 0.2 due to measurement inaccuracies of the X-ray powder diffraction experiments. Finally, the wave numbers given herein include variations of ± 3 cm $^{-1}$ due to measurement inaccuracies of the Raman experiments.

The present invention also provides a Rotigotine drug substance comprising at least about 5%, more preferably at least about 10%, of the novel polymorphic form of Rotigotine as defined above.

In a preferred embodiment the Rotigotine drug substance comprises at least about 50%, more preferably at least about 70%, of the novel polymorphic form (II) of Rotigotine as defined above. Most preferably substantially all or all (100%) of the Rotigotine in the Rotigotine drug substance is present in the novel polymorphic form (II). "Substantially all" is meant to refer to a Rotigotine drug substance comprising form II wherein preferably at least 80%, more preferably at least 90%, still more preferred at least 95% of the rotigotine is present as form (II).

In the context of the present application all percentages are given by weight unless otherwise indicated.

Furthermore, the present invention provides a pharmaceutical composition which comprises the novel polymorphic form (II) of Rotigotine as defined above and at least one pharmaceutically acceptable excipient.

The present invention also provides a process for producing the novel polymorphic form (II) of Rotigotine as defined above, which comprises tempering solid Rotigotine of polymorphic form (I) for at least 10 days at 40°C.

In said tempering process Rotigotine of polymorphic form (I) can either be in the dry state or in slurry state. When in slurry state, the slurry is preferably prepared in cyclohexane or ethanol.

In another preferred embodiment of the present invention the novel polymorphic form (II) of Rotigotine as defined above is quantitatively produced by spiking Rotigotine of polymorphic form (I) in slurry state with crystals of Rotigotine of polymorphic form (II) obtained from the tempering process or from ethanolic precipitation.

In another embodiment of the present invention the novel polymorphic form (II) of Rotigotine as defined above is quantitatively produced by spiking Rotigotine of polymorphic form (I) in dry state at 40°C with crystals of Rotigotine of polymorphic form (II). The form (II) seed crystals used may be obtained from ethanolic slurry experiments, ethanolic precipitation or from another tempering process.

In an another aspect of the present invention the novel polymorphic form (II) of Rotigotine as defined above is used for treating a patient suffering from a disease sensitive to the treatment with D2 receptor agonists.

In various embodiments of the present invention the novel polymorphic form (II) of Rotigotine as defined above is used for treating a patient suffering from Parkinson's Disease, Parkinson's plus syndrome, depression, fibromyalgia or
5 restless-legs syndrome.

Brief description of drawings

Figure 1 Experimental powder X-ray diffractogram of novel
10 polymorphic form (II) of Rotigotine

Figure 2 H-bonded polymeric (Zig-Zag) chain of Rotigotine molecules in novel polymorphic form (II) crystals

15 Figure 3 H-bonded polymeric (Zig-Zag) chain of Rotigotine molecules in polymorphic form (I) crystals

Figure 4 Experimental powder X-ray diffractogram of
20 polymorphic form (I) of Rotigotine

Figure 5 Raman spectrum of novel polymorphic form (II) of Rotigotine

Figure 6 Overlay of the Raman spectra of novel polymorphic
25 form (II) and polymorphic form (I) of Rotigotine

Figure 7 DSC thermogram of novel polymorphic form (II) of Rotigotine

30 Figure 8 DSC thermogram of polymorphic form (I) of Rotigotine

Detailed description of the invention

The invention relates to a novel crystalline form of ((-)-
5 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol), denoted herein as form II. Form II differs from form I in the structure of the crystal lattice of ((-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol), and the two forms give distinctive X-ray
10 powder diffraction (XRD) patterns, Raman Spectra and differential scanning calorimetry (DSC) thermograms.

Form I of Rotigotine is characterized by an XRD pattern comprising a peak at about 20.23 ± 0.2 ($^{\circ}2\theta$).

15 Characterization of form II and distinguishing the same from form I are accomplished using techniques known to those of skill in the art. Specifically, verification that form II is present can be performed using techniques such as melting
20 point, infrared (IR) spectroscopy, solid state nuclear magnetic resonance (SSNMR) or Raman spectroscopy. Techniques including differential scanning calorimetry (DSC) and X-ray diffraction (XRD) are also useful in distinguishing polymorphs, and specifically form II from form I. One or more
25 of the foregoing techniques can be used to identify a polymorphic form of Rotigotine.

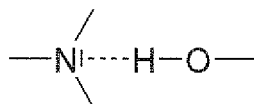
Form I and form II have distinctive characteristic peaks in their X-ray powder diffraction patterns as provided in
30 Figures 1 and 4. At least one of these peaks, and preferably a majority of these peaks, will be present in the X-ray powder diffraction pattern for a given form.

In one embodiment of the invention the XRD pattern of form II
35 exhibits a characteristic peak at 13.68 ± 0.2 ($^{\circ}2\theta$), in another embodiment the XRD pattern of form II exhibits a characteristic peak at 17.72 ± 0.2 ($^{\circ}2\theta$) and in still another

embodiment the XRD pattern of form II exhibits a characteristic peak at 19.01 ± 0.2 ($^{\circ}2\theta$). Preferably, the XRD pattern of form II exhibits characteristic peaks at 13.68 and 17.72 ± 0.2 ($^{\circ}2\theta$). More preferably, the XRD pattern of form II can comprise peaks at 13.68, 17.72 and 19.01 ± 0.2 ($^{\circ}2\theta$).

The novel polymorphic form (II) of Rotigotine ((-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol) is characterized by a powder X-ray diffractogram comprising peaks at one or more of 12.04, 12.32, 12.97, 13.68, 17.13, 17.72, 19.01, 20.40, 20.52, 21.84, 21.96, 22.01, 22.91 and 22.96 ± 0.2 ($^{\circ}2\theta$), measured with a Cu- K_{α} irradiation (1.54060 Å). In particular, the novel polymorphic form (II) of Rotigotine is characterized by at least one of the following X-ray powder diffraction peaks: 12.04, 13.68, 17.72 and 19.01 ± 0.2 ($^{\circ}2\theta$), measured with a Cu- K_{α} irradiation (1.54060 Å) (Figure 1).

The crystal lattice comparison between the novel polymorphic form (II) and polymorphic form (I) (Figures 2 and 3) shows that the main intermolecular hydrogen bonds are similar in the two cases:



However, a drastic conformational difference is observed for the torsion angle of the thiophene ring with respect to the adjacent $\text{CH}_2\text{-CH}_2$ chain. It is this approximately 100° difference (torsion angle) between the two conformational polymorphs that leads to a denser packing and a change in crystal symmetry.

The results of the crystal lattice comparison are summarized in the following table:

		Form (I)	Form (II)
Crystal system		Tetragonal	Orthorhombic
Space group		P 4 ₃	P 2 ₁ 2 ₁ 2 ₁
Unit cell dimension	Cell length [Å]	a 8.2030(10)	a 8.4310(10)
		b 8.2030(10)	b 13.620(2)
		c 26.899(5)	c 14.868(2)
	Cell angle [°]	α 90	α 90
		β 90	β 90
		γ 90	γ 90
	Cell volume [Å ³]	1810.01	1707.3
		Z: 4 Z': 0	Z: 4 Z': 0
Density (calculated) [g/cm ³]		1.158	1.227

These results are supported by the different solubility of the two polymorphs in EtOH. The solubility at room temperature of polymorphic form (I) of Rotigotine in EtOH is about 500mg/mL (1:2 [w/w]), whereas the solubility of the novel polymorphic form (II) of Rotigotine in EtOH is about 60-100mg/mL (0,6-1:10 [w/w]), i.e. the solubility of the novel polymorphic form (II) of Rotigotine in EtOH is at least five times lower than the solubility of polymorphic form (I) of Rotigotine in EtOH.

The crystallographic differences between the two polymorphic forms of Rotigotine further become apparent when comparing their X-ray diffractograms as shown in Figures 1 and 4.

The novel polymorphic form (II) of Rotigotine can be also characterized by its Raman spectrum (Figure 5).

Further, differential scanning calorimetry (DSC) data reveal the difference between the two polymorphic forms of Rotigotine (Figures 7 and 8). Basically, the novel polymorphic form (II) of Rotigotine exhibits both a higher melting point and a higher enthalpy of fusion, and by applying the Burger-Ramberger rules, it could be stated that

form (II) is thermodynamically more stable than form (I) at any temperature considered. Therefore, the two polymorphs of Rotigotine appear to be monotropically related.

5 Polymorph form II of Rotigotine can be further characterized and distinguished from form I by differential scanning calorimetry (DSC). A DSC thermogram of form II is provided in Figure 7, and was obtained using DSC techniques known to those of skill in the art. One of skill in the art would
10 readily be able to determine the conditions necessary to obtain a DSC thermogram of form II. A variety of differential scanning calorimeters are available to those of skill in the art and include the Differential-Scanning-Calorimeter from Mettler Toledo (DSC822e) using temperatures of about 25°C to
15 about 250°C, in particular about 30°C to about 140°C and temperature increases at various rates including 1°C/min, 10°C/min, 20°C/min, among other instruments and conditions. One skilled in the art would recognize that the peak positions in the DSC thermogram can vary depending upon
20 kinetic factors such as, for example, heating rate and particle size.

The DSC thermogram of form II differs from the DSC thermogram of form I and includes a peak with a T_{onset} of about 97°C ± 2°C. The DSC thermogram of form I differs from the DSC
25 thermogram of form II and includes a peak with a T_{onset} of about 77°C ± 2°C.

The novel polymorphic form (II) of Rotigotine can be prepared
30 by the following processes. In these processes, "Rotigotine" means the free base, i.e., (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol.

The novel polymorphic form (II) of rotigotine can
35 illustratively be prepared by the following processes.

(i) Preparation of the novel polymorphic form (II) of Rotigotine by tempering comprises:

- Placing Rotigotine of polymorphic form (I) in an aluthene bag
- Sealing and storing the bag at 38-40°C for 10 days

(ii) Preparation of the novel polymorphic form (II) of Rotigotine from an ethanolic slurry comprises:

- Slurrying Rotigotine of polymorphic form (I) in ethanol
- Stirring for 2h at 50 to 150rpm
- Optionally spiking of the ethanolic slurry of Rotigotine of polymorphic form (I) with Rotigotine of polymorphic form (II)
- Stirring for another 24h at 50 to 150rpm at room temperature
- Filtration of the slurry
- Drying of Rotigotine of polymorphic form (II) to constant weight

The crystalline form of Rotigotine may be prepared substantially as a single polymorph, i.e., for example comprising more than 95% of form II, or may be crystallized in combination with form I or other polymorphs. In some embodiments, the crystalline form of Rotigotine comprises at least 50% of form II. In some embodiments, the crystalline form of Rotigotine comprises at least 70% of form II. In some embodiments, the crystalline form of Rotigotine comprises at least 80% of form II. In still other embodiments, the crystalline form of Rotigotine comprises at least 90% of form II.

Rotigotine polymorphic form (II) can be used as a therapeutic active substance.

When Rotigotine of novel polymorphic form (II) is used for treating a patient suffering from a disease sensitive to the treatment with D1/D2/D3 dopamine agonists, in particular D2 receptor agonists, it may be orally or parenterally administered. In general, it is parenterally administered, e.g. in the form of a transdermal therapeutic system (TTS), by injection, such as in the form of a depot suspension, by an iontophoretic device or in the form of an intranasal formulation.

Diseases that are generally treated with Rotigotine of the novel polymorphic form (II) are Parkinson's Disease, Parkinson's plus syndrome, depression, fibromyalgia and restless-legs syndrome. The respective dose will vary depending upon symptoms, age, sex, weight and sensitivity of the patients, the method of administration, time and intervals of administration and pharmaceutical preparations, etc. Hence, there is no particular limitation with respect to the dose.

Pharmaceutical preparations containing the novel polymorphic form (II) of Rotigotine such as transdermal therapeutic systems, injections or tablets etc. are prepared according to methods commonly known in the state of the art.

The invention and the best mode for carrying it out will be explained in more detail in the following non-limiting examples.

Examples

[Preparation]

Preparation example 1

A sample of the polymorphic form (I) of Rotigotine batch 16208652 was placed in a small Aluthene® bag (2006 fabrication Bischoff+Klein). The sample was sealed and stored

at 38-40°C for 10 days. After this incubation time 1g of the sample was dissolved in 2g of EtOH, whereupon strong precipitation of form II occurred.

5 Preparation example 2

5.277kg of polymorphic form (I) of Rotigotine (batch SPM 5904) were charged in a 20L plastic bottle and converted with 5.3L EtOH in an ethanolic slurry. The slurry was transferred into a nitrogen flushed reactor and the plastic bottle was
10 rinsed with further 8.1L EtOH. The rinsing liquid was as well transferred to the reactor and the resulting suspension was stirred for 24h at 75rpm at room temperature. Subsequently, the crystal slurry was discharged from the reactor via a glass suction filter. The reactor was then rinsed with 2.6L
15 of EtOH and afterwards the rinsing liquid was used to wash the obtained filtrate. Finally, the filtrate was transferred to four tared metal sheets and dried for 43h at 40°C to constant weight.

20 In both examples the successful formation Rotigotine of polymorphic form (II) was confirmed by analytical data from DSC and XRD.

In addition, polymorphic form (I) of Rotigotine could be
25 quantitatively transformed into polymorphic form (II) of Rotigotine in a process according to preparation example 2, when the ethanolic slurry of polymorphic form (I) was spiked with seeds of Rotigotine of polymorphic form (II).

30 [Characterization of the novel polymorphic form (II) of Rotigotine in comparison to polymorphic form (I) of Rotigotine]

Single Crystal X-ray diffraction

35 Suitable single crystals for diffraction have been obtained by rapid evaporation of a methanol solution of rotigotine

polymorphic form (II) reference batch 7769396. Single crystal X-Ray diffraction data (OXFORD Gemini R Ultra, Mo-K α irradiation (0.71073 Å)) are as follows: C₁₉H₂₅NOS, M= 315.46, Orthorhombic P 2₁2₁2₁, a = 8.4310(10)Å, b = 13.620(2)Å, c = 14.868(2)Å, $\alpha=\beta=\gamma$ 90°, V[Å³]= 1707.3, Z= 4, D_c [g/cm³]= 1.227, λ = 1.54178 Å. Final disagreement factor R is 4%.

Cohesive forces of the crystal packing of polymorphic form (II) of Rotigotine are mainly made up of polymeric zig-zag chains of hydrogen bonds via the basic nitrogen atom (N1) and the phenol oxygen (O1).

This structure determination confirms that polymorphic form (II) is a true polymorph of Rotigotine and confirms the occurrence of conformational polymorphism.

The structure determination of polymorphic form (II) of Rotigotine allows to simulate a theoretical powder X-ray pattern (Mercury 1.5) characterized by the following peaks: 8.82, 12.06, 12.34, 13, 13.7, 14.32, 17.18, 17.76, 19.04, 20.44, 22.06, 23.02, 24.26 and 27.76 (°2 θ).

Experimental X-ray Powder Diffraction

The X-ray analysis was performed on a STOE STADI-P powder diffraction System with a Cu-K α irradiation (1.54060 Å), wherein it was shown that the experimental pattern of polymorphic form (II) of Rotigotine perfectly matches with its simulated powder pattern.

In accordance with embodiments of the invention, the XRD patterns of form I and form II contain peaks that are specific for each form. The XRD pattern of form II contains peaks not present in the XRD pattern of form I, and includes a peak at about 17.72 $\pm$ 0.2 (°2 θ). In another embodiment, the XRD pattern of form II differs from the XRD pattern of form I and includes a peak at about 13.68 $\pm$ 0.2 (°2 θ). In another embodiment, the XRD pattern of form II differs from the XRD

pattern of form I and includes a peak at about 19.01 ± 0.2 ($^{\circ}2\theta$). In another embodiment, the XRD pattern of form II differs from the XRD pattern of form I and includes peaks at about 17.72 ± 0.2 ($^{\circ}2\theta$) and 19.01 ± 0.2 ($^{\circ}2\theta$). Importantly, the XRD pattern of form II lacks a peak at about 20.23 ± 0.2 ($^{\circ}2\theta$).

The results furthermore clearly demonstrate the difference between the two Rotigotine polymorphs (Figures 1 and 4). The experimental X-ray diffraction pattern of the novel polymorphic form (II) of Rotigotine is characterized by peaks at diffraction angles ($^{\circ}2\theta$) of 12.04, 12.32, 12.97, 13.68, 17.72, 19.01, 20.40, 20.52, 21.84, 21.96, 22.01, 22.91 and 22.96, whereas the experimental pattern of polymorphic form (I) is characterized by peaks at diffraction angles ($^{\circ}2\theta$) of 10.83, 12.68, 14.66, 15.32, 16.66, 16.68, 20.23, 22.67, 25.17, 25.47, 26.27, 27.75, and 29.55. Each of these peaks, either alone or in combination with others, may be taken as a basis to characterize Rotigotine of form (I) or form (II), respectively.

Raman Spectroscopy

A sample of Rotigotine was placed on a cover glass and then, based on only one crystal, the sample was focalized with 10x and 50x-WD: Raman HJY ARAMIS, laser 784.9 nm, 4x 20 sec, obj. 10X + 50X-WD, hole 500 μ m, slit 100 μ m. The acquisition was performed by 4x 20 seconds with the objective 50x-WD.

The results are shown in Figures 5 and 6. Figure 5 represents the spectrum of polymorphic form (II) of Rotigotine whereas Figure 6 shows the superimposition of batches 7769396 (reference polymorphic form (II)) and WE 11664 PS-7 (predominantly polymorphic form (I)). This overlay highlights several discriminative peaks of these two batches. The novel polymorphic form (II) of Rotigotine comprises at least one peak, preferably at least two peaks, at least three or at least four peaks at wave numbers (cm^{-1}) selected from 226.2,

297.0, 363.9, 710.0, 737.3, 743.3, 750.8, 847.3, 878.3, 1018.7, 1075.6, 1086.2, 1214.3, 1255.1, 1278.2, 1330.7, 1354.3 and $1448.7 \pm 3 \text{ cm}^{-1}$ whereas polymorphic form (I) exhibits characteristic peaks at wave numbers (cm^{-1}) of 238.4, 277.3, 307.6, 445.9, 682.6, 747.2, 882.2, 1027.2, 1039.4, 1081.6 and $1324.3 \pm 3 \text{ cm}^{-1}$. The novel polymorphic form (II) of Rotigotine ((-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol) is characterized by a Raman spectrum comprising at least one peak, preferably at least two, at least three or at least four peaks at wave numbers (cm^{-1}) selected from 710.0, 737.3, 743.3, 847.3, 1018.7, 1214.3, 1278.2, 1354.3 $\pm 3 \text{ cm}^{-1}$. In particular, the novel polymorphic form (II) of Rotigotine is characterized by at least one of the following peaks: 226.2, 297.0, 363.9, 737.3, 847.3, 1018.7 and $1354.3 \pm 3 \text{ cm}^{-1}$.

Differential Scanning Calorimetry (DSC)

Thermal behavior investigations of Rotigotine of polymorphic form (I) (batch 1608726) and of polymorphic form (II) (batch 7769396) were performed on a Mettler Toledo DSC system and on a TA instrument (Q-1000). The analyses were carried out with a heating rate of $10^\circ\text{C}/\text{min}$ in pierced aluminum crucibles in a temperature range from 30°C to 140°C .

The results are summarized in Figure 7 and Figure 8. The DSC thermogram of the novel polymorphic form (II) exhibits an endothermic peak with a T_{onset} at $97 \pm 2^\circ\text{C}$ and a T_{peak} at $98^\circ\text{C} \pm 2^\circ\text{C}$, whereas the onset of the endothermic peak of polymorphic form (I) is at $77 \pm 2^\circ\text{C}$ under the same conditions. For both polymorphs only one single peak could be observed in their thermograms, indicating said polymorphs being free of any impurities of the respective other polymorph, with respect to DSC sensitivity.

In sum, the two polymorphic forms of Rotigotine can be differentiated by their respective melting point and their respective enthalpy of fusion. Both are higher for the novel

polymorphic form (II) and by applying the Burger-Ramberger rules, it could be demonstrated that polymorphic form (II) is thermodynamically more stable than polymorphic form (I) at all considered temperatures. Therefore, the two polymorphs of
5 Rotigotine are most probably monotropically related.

The melting point of the novel polymorphic form (II) of Rotigotine can also be measured with the capillary method (in an oil/water bath with a magnifier) or with a Kofler
10 Hotbench.

Claims

- 5 1. Polymorphic form (II) of Rotigotine ((-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol).
- 10 2. A polymorphic form of Rotigotine having at least one of
- a X-ray powder diffraction spectrum comprising at least one peak at the following $^{\circ}2\theta$ angles (± 0.2): 12.04, 13.68, 17.72, 19.01
- 15 a Raman spectrum comprising at least one peak at the following wave numbers ($\pm 3 \text{ cm}^{-1}$): 226.2, 297.0, 363.9, 737.3, 847.3, 1018.7, 1354.3 cm^{-1} ;
- 20 a DSC peak with a T_{onset} at $97^{\circ}\text{C} \pm 2^{\circ}\text{C}$ measured with a heating rate of $10^{\circ}/\text{min}$;
- a melting point of $97^{\circ}\text{C} \pm 2^{\circ}\text{C}$.
- 25 3. A polymorphic form of Rotigotine according to claim 2, characterized by two, three or four of the following X-ray powder diffraction peaks ($^{\circ}2\theta$) (± 0.2): 12.04, 13.68, 17.72, 19.01.
- 30 4. A polymorphic form of Rotigotine having a X-ray powder diffraction spectrum substantially as shown in Figure 1.
5. Rotigotine drug substance comprising at least 5%, more preferably at least 10%, of a polymorphic form of Rotigotine as defined in any one of claims 1-4.

6. A Rotigotine drug substance comprising at least 50%, more preferably at least 90%, of a polymorphic form of Rotigotine as defined in any one of claims 1-4.

5 7. A Rotigotine drug substance wherein substantially all of Rotigotine is in a polymorphic form as defined in any one of claims 1-4.

8. A crystalline polymorph according to any of claims 1 to
10 7 for use as therapeutic active substance.

9. Pharmaceutical composition comprising a Rotigotine drug substance according to claims 5-7 and at least one pharmaceutically acceptable excipient.

15 10. A pharmaceutical composition according to claim 9, wherein the rotigotine drug substance comprises at least 5% of said polymorphic form of rotigotine as defined in any one of claims 1-4.

20 11. The pharmaceutical composition according to claim 9 or 10, which is in form of a transdermal therapeutic system.

12. Polymorphic form of Rotigotine as defined in any of
25 claims 1-4 for use in a method for treating a patient suffering from a disease sensitive to the treatment with D2 receptor agonists.

13. Polymorphic form of Rotigotine as defined in any of
30 claims 1-4 for use in a method for treating a patient suffering from a disease sensitive to the treatment with D2 receptor agonists, wherein said disease is selected from Parkinson's Disease, Parkinson's plus syndrome, depression, fibromyalgia and/or restless-legs syndrome.

35 14. Use of a polymorphic form of Rotigotine as defined in any of claims 1-4 for the manufacture of a medicament for the

treatment of a patient suffering from a disease sensitive to the treatment with D2 receptor agonists.

15. Use according to claim 13, wherein the disease sensitive
5 to the treatment with D2 receptor agonists is selected from Parkinson's Disease, Parkinson's plus syndrome, depression, fibromyalgia and/or restless-legs syndrome.