



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## Spedra

### Procedural steps taken and scientific information after the authorisation

| Application number  | Scope                                                                                                      | Opinion / Notification <sup>1</sup> issued on | Commission Decision Issued <sup>2</sup> / amended on | Product Information affected <sup>3</sup> | Summary                                                                                                                                    |
|---------------------|------------------------------------------------------------------------------------------------------------|-----------------------------------------------|------------------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| PSUSA/10066 /202306 | Periodic Safety Update EU Single assessment - avanafil                                                     | 22/02/2024                                    | 19/04/2024                                           | SmPC and PL                               | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10066/202306. |
| IB/0036             | B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation | 10/07/2023                                    | n/a                                                  |                                           |                                                                                                                                            |

<sup>1</sup> Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.

<sup>2</sup> A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.

<sup>3</sup> SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).



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| N/0035              | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 04/11/2021 | 19/04/2024 | PL                     |                                   |
| PSUSA/10066 /202006 | Periodic Safety Update EU Single assessment - avanafil                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 11/02/2021 | n/a        |                        | PRAC Recommendation - maintenance |
| IB/0033/G           | <p>This was an application for a group of variations.</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms</p> <p>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</p> <p>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</p> <p>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</p> <p>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</p> <p>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</p> | 27/10/2020 | 19/10/2021 | SmPC, Labelling and PL |                                   |

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|           | <p>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</p> <p>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</p> <p>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</p> <p>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</p> <p>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes</p> |            |     |  |  |
| IB/0032/G | <p>This was an application for a group of variations.</p> <p>A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient</p> <p>B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 24/09/2020 | n/a |  |  |

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|           | data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |     |  |  |
| IA/0031   | A.7 - Administrative change - Deletion of manufacturing sites                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 30/04/2020 | n/a |  |  |
| IB/0030/G | <p>This was an application for a group of variations.</p> <p>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate</p> <p>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate</p> <p>B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products</p> <p>B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of</p> | 27/01/2020 | n/a |  |  |

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|        | <p>the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p> |            |            |                                  |                                                                                                                                                                                                                               |
| R/0029 | Renewal of the marketing authorisation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 22/02/2018 | 23/04/2018 | SmPC, Annex II, Labelling and PL | Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Spedra in the approved indication remains favourable and therefore recommended the renewal of the marketing |

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|                     |                                                                                                                                                                                                                                                                                                             |            |            |             | authorisation with unlimited validity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| PSUSA/10066 /201706 | Periodic Safety Update EU Single assessment - avanafil                                                                                                                                                                                                                                                      | 11/01/2018 | n/a        |             | PRAC Recommendation - maintenance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| II/0027/G           | <p>This was an application for a group of variations.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 09/11/2017 | 23/04/2018 | SmPC and PL | <p>In clinical trial TA-401 performed in healthy volunteers and adult males with mild erectile dysfunction, the daily administration of avanafil 100 mg oral doses over a period of 26 weeks was not associated with any untoward effects on sperm concentration, count, motility, or morphology.</p> <p>In study TA-402, no remarkable findings in visual acuity, pupillometry, colour vision discrimination, and intraocular pressure were observed in subjects treated with Spedra. The information already included in section 4.4 of the SmPC regarding non-arteritic anterior ischaemic optic neuropathy (NAION) and the advice to the patients that suddenly loss the vision to consult a physician is considered sufficient</p> |
| N/0026              | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)                                                                                                                                                                                                            | 24/03/2017 | 23/04/2018 | PL          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PSUSA/10066 /201606 | Periodic Safety Update EU Single assessment - avanafil                                                                                                                                                                                                                                                      | 12/01/2017 | n/a        |             | PRAC Recommendation - maintenance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| IB/0025             | B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation                                                                                                                                                                                                  | 09/11/2016 | n/a        |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| IB/0023             | B.I.a.3.d - Change in batch size (including batch size ranges) of AS or intermediate - More than 10-fold increase compared to the originally approved batch size                                                                                                                                            | 16/06/2016 | n/a        |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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| IB/0022             | B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)                                                                                                                                                                                                                                                                                                                                   | 07/04/2016 | n/a        |                     |                                                                                                                                                                                                                                              |
| IB/0021             | B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)                                                                                                                                                                                                                                                                                                                                | 10/03/2016 | 05/12/2016 | SmPC                |                                                                                                                                                                                                                                              |
| IA/0020             | B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size                                                                                                                                                                                                                                                                                                             | 29/02/2016 | n/a        |                     |                                                                                                                                                                                                                                              |
| II/0019             | <p>Update of section 4.5 of the SmPC with information on inhibition of drug transporters, thus addressing the recommendation at the conclusion of the assessment of REC 003.2. Minor corrections are made in section 4.5 of the SmPC and the contact details of the Bulgarian local representative in the Package Leaflet are also updated.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 25/02/2016 | 05/12/2016 | SmPC and PL         | <p>Based on in vitro data, at clinically relevant concentrations avanafil could be an inhibitor of BCRP.</p> <p>At clinically relevant concentrations avanafil is not an inhibitor of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3 and BSEP.</p> |
| PSUSA/10066 /201506 | Periodic Safety Update EU Single assessment - avanafil                                                                                                                                                                                                                                                                                                                                                                                                                   | 14/01/2016 | n/a        |                     | PRAC Recommendation - maintenance                                                                                                                                                                                                            |
| IB/0018             | B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g.                                                                                                                                                                                                                                                                                                                                                                         | 16/12/2015 | 05/12/2016 | SmPC, Labelling and |                                                                                                                                                                                                                                              |

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|                     | tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |            |            | PL              |                                                                                                                                                              |
| II/0012             | B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 19/11/2015 | n/a        |                 |                                                                                                                                                              |
| PSUSA/10066 /201412 | Periodic Safety Update EU Single assessment - avanafil                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 23/07/2015 | 18/09/2015 | SmPC and PL     | Please refer to Spedra-PSUSA/00010066/201412 EPAR: Scirntific conclusions and grounds recommending the variation to the terms of the marketing authorisation |
| IB/0016/G           | <p>This was an application for a group of variations.</p> <p>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site</p> <p>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site</p> <p>B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products</p> <p>B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of</p> | 08/05/2015 | 18/09/2015 | Annex II and PL |                                                                                                                                                              |



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|         | <p>the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p> |            |            |             |                                                                                                                                                                                                           |
| IA/0014 | A.6 - Administrative change - Change in ATC Code/ATC Vet Code                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 06/03/2015 | 18/09/2015 | SmPC        |                                                                                                                                                                                                           |
| IA/0013 | A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 04/02/2015 | n/a        |             |                                                                                                                                                                                                           |
| II/0007 | Update of sections 4.2 and 5.1 of the SmPC further to the results of clinical study TA-501 conducted to examine the onset of the therapeutic effects of avanafil after dosing in men with mild to severe                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 18/12/2014 | 22/01/2015 | SmPC and PL | Study TA-501 investigated the onset of action of avanafil at two doses (100 and 200 mg) in terms of per-subject proportion of sexual attempts resulting in satisfactory completion of sexual intercourse. |

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|           | <p>erectile dysfunction. The Package leaflet is updated accordingly. In addition, the MAH takes the opportunity to delete the warning on arrhythmia included in the Package Leaflet to bring it in line with the SmPC and to make minor editorial changes.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>                                                                                                                                 |            |     |  | <p>Avanafil demonstrated statistically significant improvement in the primary efficacy variable (average per subject proportion of successful responses by time after dose administration, to the Sexual Encounter Profile 3 - SEP3) as compared with placebo, resulting in successful intercourse in 24.71% of the attempts for the 100 mg dose and 28.18% for the 200 mg dose at approximately 15 minutes after dosing compared to 13.78% for placebo.</p> <p>Consequently, the posology of avanafil in section 4.2 of the SmPC is amended to for the recommended dose of 100 mg to be taken as needed approximately 15-30 minutes before sexual activity (see section 5.1 of the SmPC).</p> |
| PSUV/0010 | Periodic Safety Update                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 09/01/2015 | n/a |  | PRAC Recommendation - maintenance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| IB/0011   | B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF                                                                                                                                                                                                                                                                                                                                                                                                             | 04/11/2014 | n/a |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| IB/0008/G | <p>This was an application for a group of variations.</p> <p>B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF</p> <p>B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.c - Change in the specification parameters</p> | 18/09/2014 | n/a |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

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|         | <p>and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method</p> <p>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS</p> |            |     |  |  |
| IA/0009 | B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 09/09/2014 | n/a |  |  |

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| PSUV/0005   | Periodic Safety Update                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 10/07/2014 | n/a        |                        | PRAC Recommendation - maintenance                                                                      |
| IB/0006     | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 25/04/2014 | n/a        |                        |                                                                                                        |
| IB/0003     | B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 24/02/2014 | n/a        |                        |                                                                                                        |
| IAIN/0004/G | <p>This was an application for a group of variations.</p> <p>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site</p> <p>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site</p> <p>B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing</p> <p>C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location</p> | 03/02/2014 | 22/01/2015 | Annex II and PL        |                                                                                                        |
| IB/0002     | B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 13/01/2014 | 22/01/2015 | SmPC                   |                                                                                                        |
| T/0001      | Transfer of Marketing Authorisation from VIVUS BV to Menarini International Operations Luxembourg S.A.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 06/09/2013 | 02/10/2013 | SmPC, Labelling and PL | Transfer of Marketing Authorisation from VIVUS BV to Menarini International Operations Luxembourg S.A. |

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|  | Transfer of Marketing Authorisation |  |  |  |  |
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