# Ammonaps

Procedural steps taken and scientific information after the authorisation

| Application number | Scope | Opinion/ Notification [1] issued on | Commission Decision Issued [2] / amended on | Product Information affected [3] | Summary |
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| IAIN/0063 | A.1 - Administrative change - Change in the name and/or address of the MAH | 12/12/2022 | | SmPC, Labelling and PL | |
| PSUSA/2758/ 202112 | Periodic Safety Update EU Single assessment - sodium phenylbutyrate | 01/09/2022 | n/a | | PRAC Recommendation - maintenance |
| IA/0061 | B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier | 07/03/2022 | n/a | | |

[1] 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.
[2] 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.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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| IB/0059 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 14/10/2020 | 19/10/2021 | SmPC and PL | |
| IB/0058/G | This was an application for a group of variations.<br><br>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits<br>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure<br>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 data<br>B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking<br>B.I.z - Quality change - Active substance - Other variation | 09/07/2020 | n/a | | |
| PSUSA/2758/ 201812 | Periodic Safety Update EU Single assessment - sodium phenylbutyrate | 05/09/2019 | n/a | | PRAC Recommendation - maintenance |
| T/0057 | Transfer of Marketing Authorisation | 03/05/2019 | 06/06/2019 | SmPC, Labelling and PL | |
| IAIN/0055/G | This was an application for a group of variations. | 15/03/2019 | 06/06/2019 | Annex II and PL | |

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| | A.7 - Administrative change - Deletion of manufacturing sites<br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing | | | | |
| T/0054 | Transfer of Marketing Authorisation | 13/12/2018 | 06/02/2019 | SmPC, Labelling and PL | |
| IB/0053/G | This was an application for a group of variations.<br><br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation<br>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site<br>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site<br>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<br>B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test | 26/10/2018 | 06/02/2019 | Annex II | |

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| | B.II.c.3.a.1 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents NOT used in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product<br>B.II.c.3.a.1 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents NOT used in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product<br>B.II.d.1.i - Change in the specification parameters and/or limits of the finished product - Ph. Eur. 2.9.40 uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 or Ph. Eur. 2.9.6<br>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation<br>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)<br>B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation<br>B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - | | | | |

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| | Other variation<br>B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation<br>B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation<br>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation<br>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation<br>B.II.e.6.z - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Other variation | | | | |
| IB/0051 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 28/06/2017 | 06/07/2018 | Annex II | |
| IAIN/0050 | B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking | 01/06/2017 | n/a | | |
| A31/0048 | Pursuant to Article 31 of Directive 2001/83/EC, the European Commission requested on 17 June 2016 the opinion of the European Medicines Agency further to the issuance of a GMP non-compliance statement for the manufacturer Pharmaceutics International, Inc. (PII), located in Maryland, USA. The CHMP was requested to assess the impact thereof on the benefit-risk balance of medicinal products for which | 15/09/2016 | 29/11/2016 | | Please refer to the assessment report: Pharmaceutics International Inc EMEA/H/A-31/1444 |

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| | the said site is included in the marketing authorisation as manufacturing site, including Ammonaps, Lutinus (and associated names), Dutasteride Actavis (and associated names) and SoliCol D3, and to give its recommendation whether the marketing authorisation of these products should be maintained, varied, suspended or revoked. | | | | |
| PSUSA/2758/ 201512 | Periodic Safety Update EU Single assessment - sodium phenylbutyrate | 02/09/2016 | n/a | | PRAC Recommendation - maintenance |
| IA/0046 | B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms | 02/03/2015 | n/a | | |
| IAIN/0045 | 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 | 08/04/2014 | n/a | | |
| IB/0044 | B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product | 03/03/2014 | 08/04/2015 | SmPC, Labelling and PL | |
| II/0043/G | This was an application for a group of variations.<br><br>Change in the specification for dissolution of the tablets,replacing the analytical procedure, and the deletion of two non-significant specification | 18/08/2011 | 22/09/2011 | | |

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| | parameters.<br><br>B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)<br>B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter | | | | |
| II/0042/G | This was an application for a group of variations.<br><br>Change in the specification for bulk density of granules and deletion of non-significant specification parameter.<br><br>B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range<br>B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter | 18/08/2011 | 13/09/2011 | SmPC and PL | |
| IA/0041 | A.7 - Administrative change - Deletion of manufacturing sites | 17/06/2011 | n/a | | |
| IB/0040/G | This was an application for a group of variations. | 15/12/2010 | n/a | | |

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| | 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<br>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site | | | | |
| IA/0039 | A.1 - Administrative change - Change in the name and/or address of the MAH | 02/12/2010 | n/a | SmPC, Labelling and PL | |
| N/0038 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 17/09/2010 | n/a | PL | |
| IB/0037 | IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance | 06/01/2010 | n/a | | |
| IB/0035 | IB_37_b_Change in the specification of the finished product - add. of new test parameter | 02/12/2009 | n/a | | |
| IB/0036 | IB_38_c_Change in test procedure of finished product - other changes | 17/11/2009 | n/a | | |
| R/0034 | Renewal of the marketing authorisation. | 23/07/2009 | 14/10/2009 | SmPC, Labelling and PL | Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Ammonaps continues to be favourable.<br><br>The CHMP is also of the opinion that the renewal can be |

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| | | | | | granted with unlimited validity.<br><br>The MAH should submit three yearly PSURs. |
| II/0031 | Change of the finished product specification.<br><br>Quality changes | 22/01/2009 | 27/01/2009 | | |
| IA/0033 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 17/11/2008 | n/a | | |
| IA/0032 | IA_09_Deletion of manufacturing site | 02/10/2008 | n/a | | |
| II/0028 | The Marketing Authorisation Holder applied for an additonal manufacturing site for the finished product (tablets and granules).<br><br>Quality changes | 24/07/2008 | 29/07/2008 | | |
| IA/0029 | IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing | 29/04/2008 | n/a | Annex II and PL | |
| IA/0030 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 25/04/2008 | n/a | | |
| IB/0024 | IB_10_Minor change in the manufacturing process of the active substance | 30/01/2008 | n/a | | |
| IA/0027 | IA_23_b_Change in source of excip./reagent to veg./synthetic material - other cases | 17/01/2008 | n/a | | |

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| IB/0025 | IB_12_b_01_Change in spec. of active subst./agent in manuf. of active subst. - test parameter AS | 10/01/2008 | n/a | | |
| II/0023 | Update of the sections 2, 4, 5, 6.6, 8, 9 and 10 of the Summary of Product Characteristics, the Annex II, the Labelling and each section of the Package Leaflet in accordance with the latest version of the QRD-template. The Marketing Authorisation Holder took this opportunity to also implement some minor editorial changes to improve the readability of the set of Annexes.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet | 20/09/2007 | 31/10/2007 | SmPC, Annex II, Labelling and PL | The Marketing Authorisation Holder applied for an update of the sections 2, 4.2, 4.3, 4.4, 4.6, 4.8, 4.9, 5.1, 5.2, 6.6, 8, 9 and 10 of the Summary of Product Characteristics, of the Annex II, Labelling and each section of the Package Leaflet in accordance with the current version of the QRD-template. No new quality, safety or efficacy data was submitted by the Marketing Authorisation Holder during this procedure. |
| II/0022 | Change to the storage conditions of Ammonaps granules with resulting amendments to section 6.4 of the SPC, and to the labelling and package leaflet.<br><br>Quality changes | 24/05/2007 | 03/07/2007 | SmPC, Annex II, Labelling and PL | |
| IA/0021 | IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer | 02/03/2007 | n/a | | |
| IA/0020 | IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer | 02/03/2007 | n/a | | |
| IB/0018 | IB_33_Minor change in the manufacture of the finished product | 23/11/2006 | n/a | | |
| IA/0017 | IA_09_Deletion of manufacturing site | 29/06/2006 | n/a | Annex II and PL | |

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| T/0016 | Transfer of Marketing Authorisation | 30/03/2006 | 24/04/2006 | SmPC, Annex II, Labelling and PL | |
| IB/0015 | IB_33_Minor change in the manufacture of the finished product | 02/02/2006 | n/a | | |
| IA/0014 | IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing | 15/11/2005 | n/a | Annex II and PL | |
| IA/0013 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 15/11/2005 | n/a | | |
| R/0012 | Renewal of the marketing authorisation. | 15/12/2004 | 31/03/2005 | SmPC, Labelling and PL | |
| II/0011 | Update of Summary of Product Characteristics and Package Leaflet | 16/09/2004 | 28/10/2004 | SmPC and PL | |
| S/0008 | annual re-assessment | 26/02/2004 | 06/07/2004 | Annex II and PL | The benefit/risk profile of Ammonaps remains favourable. After having re-assessed the data submitted by the MAH the CPMP recommended that the Community Marketing Authorisation under exceptional circumstances should be lifted, as there were no remaining chemical/pharmaceutical and clinical Specific Obligations to be fulfilled. |
| II/0006 | This variation concerns an update to section 4.9 of the SPC following assessment of the PSUR 5.<br><br>Update of Summary of Product Characteristics | 25/09/2003 | 27/01/2004 | SmPC | The section 4.8 of the SPC was updated with the following information on overdose: One case of overdose occurred in a 5-month old infant with an accidental single dose of 10 g (1370 mg/kg). He developed diarrhoea, irritability, metabolic acidosis with hypokalaemia and recovered within 48 hours |

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| | | | | | after symptomatic treatment. These symptoms are consistent with the accumulation of phenylacetate, which showed dose-limiting neurotoxicity when administered intravenously at doses up to 400 mg/kg/day. Manifestations were predominantly somnolence, fatigue and light-headedness; less frequent were: confusion, headache, dysgeusia, hypacusis, disorientation, impaired memory and exacerbation of a pre-existing neuropathy. |
| IA/0010 | IA_09_Deletion of manufacturing site | 19/12/2003 | n/a | Annex II and PL | |
| I/0007 | IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening | 18/11/2003 | n/a | | |
| S/0005 | annual re-assessment | 25/04/2003 | 22/07/2003 | Annex II | It was concluded that them overall the risk/benefit profile remains unchanged, but that the marketing authorisation should be maintained under exceptional circumstances as a number of residual issues are still pending. |
| S/0004 | annual re-assessment | 21/02/2002 | 29/04/2002 | | It was concluded that them overall the risk/benefit profile remains unchanged, but that the marketing authorisation should be maintained under exceptional circumstances as a number of residual issues are still pending. |
| II/0002 | Update of or change(s) to the pharmaceutical documentation | 18/10/2001 | 14/02/2002 | | |
| S/0003 | Annual re-assessment. | 25/01/2001 | 06/06/2001 | Annex II | |
| I/0001 | 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process | 20/09/2000 | 15/01/2001 | Annex II and PL | |