Methylthioninium chloride Proveblue

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
IB/0064/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters	26/11/2024	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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	and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0063	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	16/08/2024	n/a		
N/0062	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/03/2024	17/05/2024	PL	
IB/0061	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	27/02/2024	n/a		
IB/0059	B.II.f.1.b.z - Stability of FP - Extension of the shelf life of the finished product - Other variation	31/01/2024	17/05/2024	SmPC	
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/01/2024	17/05/2024	PL	
PSUSA/2029/ 202305	Periodic Safety Update EU Single assessment - methylthioninium chloride	11/01/2024	n/a		PRAC Recommendation - maintenance
IB/0057	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	20/07/2023	n/a		
II/0056	Update of sections 4.4 and 4.5 of the SmPC to update the warning and add information regarding the potential increase of the risk of serotonin syndrome when used in combination with opioids, as well as, to add information regarding the potent	12/05/2023	17/05/2024	SmPC and PL	Methylthioninium chloride is a known potent reversible inhibitor of monoamine oxidase and thus may cause serious or fatal serotonergic syndrome when used in combination with serotonergic drugs. Based on post-marketing and literature data, the possible increased risk of developing

	reversible monoamine oxidase (MAO) inhibitory activity of Methylthioninium chloride based on post-marketing data and literature; the Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				serotonin syndrome, was updated to also include concomitant use of Methylthioninium chloride and opioids as tramadol, fentanyl, pethidine, and dextromethorphan. For more information, please refer to the Summary of Product Characteristics.
II/0055/G	This was an application for a group of variations. B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier A.7 - Administrative change - Deletion of manufacturing sites	04/05/2023	17/05/2024	Annex II and PL	The product information has been updated as follows. The PL has been updated to reflect the removal of the Pierrel site of batch release, this has also been reflected in the annex IIA manufacturing sites.
II/0054	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/03/2023	n/a		
II/0052/G	This was an application for a group of variations. -Update of section 4.2 and 5.2 of the SmPC in order to change the posology recommendations in patients	13/10/2022	18/11/2022	SmPC, Labelling and PL	The PI was updated to change the posology recommendations in patients with renal and hepatic impairment and to add drug-drug interaction information,

	with renal and hepatic impairment and update the pharmacokinetic information respectively, based on results from: an open-label, parallel group, population-matched, single-dose study to investigate the influence of renal impairment on the pharmacokinetics of ProvayBlue (Study Report PVP-2016006). The package leaflet and labelling are updated accordingly. The MAH takes this opportunity to update the Product Information according to the QRD template v10.2. -Update of section 4.5 and 5.2 of the SmPC in order to add drug-drug interaction information with other medicinal products and update the pharmacokinetic information respectively, based on results from: an open-label, randomized, two-period, crossover study to assess the effect of a single dose of methylene blue 5 mg/ml on the pharmacokinetics of the probe drugs midazolam, caffeine, warfarin, omeprazole and dextromethorphan in healthy subjects (Study Report PVP-2016004). The package leaflet and labelling are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				updating the pharmacokinetic information respectively.
N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/09/2022	18/11/2022	PL	

N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/07/2021	18/11/2022	Labelling and PL	
PSUSA/2029/202005	Periodic Safety Update EU Single assessment - methylthioninium chloride	14/01/2021	n/a		PRAC Recommendation - maintenance
IA/0050/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	23/10/2020	n/a		
IB/0048/G	This was an application for a group of variations. 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 B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	28/04/2020	n/a		
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/02/2020	18/11/2022	PL	

IA/0046	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	06/11/2019	n/a		
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/06/2019	18/11/2022	PL	
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/04/2019	18/11/2022	PL	
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/04/2018	18/11/2022	PL	
PSUSA/2029/ 201705	Periodic Safety Update EU Single assessment - methylthioninium chloride	14/12/2017	08/02/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2029/201705.
IB/0041	B.I.z - Quality change - Active substance - Other variation	11/01/2018	n/a		
IA/0040	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	09/01/2018	n/a		
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/10/2017	08/02/2018	PL	
N/0037	Minor change in labelling or package leaflet not	11/07/2017	11/09/2017	PL	

	connected with the SPC (Art. 61.3 Notification)				
IB/0036	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	29/05/2017	n/a		
PSUSA/2029/ 201605	Periodic Safety Update EU Single assessment - methylthioninium chloride	01/12/2016	n/a		PRAC Recommendation - maintenance
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/11/2016	11/09/2017	PL	
II/0032/G	This was an application for a group of variations. Update of sections 4.5 and 5.2 of the SmPC in order to add information on drug-drug interactions based on data from clinical pharmacology studies. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	11/09/2017	SmPC	Based on the interaction studies performed, the following information has been added to sections 4.5 and 5.2 of the SmPC: Section 4.5 Methylthioninium chloride is an in vitro inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5. The clinical consequences of increases plasma concentration of co-administered drugs which are sensitive CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A substrates cannot be ruled out. Methylthioninium chloride is an in vitro inducer of CYP1A2. The clinical consequence is not known. The administration of methylthioninium chloride Proveblue has the potential to transiently increase or decrease the clearance of drugs that are primarily metabolized by these enzymes. The clinical consequences are however considered minimal since methylthioninium chloride Proveblue is used often only once and in an acute emergency setting. Methylthioninium chloride is a potent inhibitor of the

					transporters OCT2, MATE1 and MATE2-K. The clinical consequences of the inhibition are not known. The administration of methylthioninium chloride Proveblue has the potential to transiently increase the exposure of drugs primarily cleared by renal transport involving the OCT2/MATE pathway, including cimetidine, metformin and acyclovir. Methylthioninium chloride is a substrate of P-glycoprotein (P-gp). The clinical consequences are considered likely to be minimal due to the transient and single dose use that normally occurs in the emergency setting. Section 5.2 Methylthioninium chloride Proveblue is not an in vitro inducer of CYP2B6 and CYP3A4. Methylthioninium chloride Proveblue is an in vitro inhibitor of P-gp. Methylthioninium chloride Proveblue is not an in vitro substrate for BCRP or OCT2 and is not an in vitro inhibitor of BCRP, OAT1 or OAT3.
II/0030/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to include the adverse drug reactions paresthesia and dysgeusia with the frequency "very common" based on data from two clinical studies. In addition, frequencies were added in the tabulated list of adverse reactions. The Package Leaflet was updated accordingly. Furthermore, the RMP version 2.0 was updated accordingly and to implement the current RMP template.	15/09/2016	11/09/2017	SmPC and PL	Based on the clinical study data, the following two adverse reactions have been added to the Product Information with frequency "very common": paresthesia (numbness and tingling) and dysguesia (abnormal taste in mouth).

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0033/G	This was an application for a group of variations. B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	01/08/2016	n/a		
N/0031	Update of the package leaflet with revised contact details of the local representatives for Italy and Hungary. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/05/2016	11/09/2017	PL	

PSUSA/2029/201505	Periodic Safety Update EU Single assessment - methylthioninium chloride	17/12/2015	18/02/2016	SmPC and PL	Please refer to Methylthioninium chloride Proveblue PSUSA/00002029/201505 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
R/0027	Renewal of the marketing authorisation.	19/11/2015	08/02/2016	SmPC, Annex II, Labelling and PL	Methylthioninium chloride is effective in treating externally induced methaemoglobinaemia. Severe adverse events linked to methylthioninium chloride treatments are well documented and addressed in the SmPC. No new safety concerns have been identified in the 5 year period. The favourable effects of the treatment are considered to clearly outweigh the risks. The benefit risk for methylthioninium chloride in the treatment of methaemoglobinaemia remains favourable and therefore the CHMP recommends the renewal of the marketing authorisation with unlimited validity.
IB/0029	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	21/10/2015	n/a		
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/08/2015	08/02/2016	PL	
IA/0028	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	11/08/2015	n/a		
IB/0024	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	11/08/2015	n/a		

	data				
IAIN/0022	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	21/07/2015	n/a		
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/04/2015	08/02/2016	PL	
PSUSA/2029/201405	Periodic Safety Update EU Single assessment - methylthioninium chloride	04/12/2014	n/a		PRAC Recommendation - maintenance
IB/0020	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	28/10/2014	n/a		
II/0017/G	This was an application for a group of variations. This is a grouping of variations to add a new manufacturer for the active substance, to add new sites for storage and testing of the active substance and to delete two non-significant in-process tests for the active substance. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a	25/09/2014	n/a		

	starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test				
II/0015	Update of section 4.3 of the SmPC to amend the contraindication to patients with nitrite-induced methaemoglobinaemia during treatment of cyanide poisoning. The Package Leaflet is updated accordingly.	25/09/2014	16/12/2014	SmPC and PL	As a result of this variation, section 4.3 of the SmPC were updated by replacing the text "Patients with sodium nitrite-induced methaemoglobinaemia" with "Patients with nitrite-induced methaemoglobinaemia during treatment of cyanide poisoning". The Package Leaflet (PL) was updated

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				accordingly.
II/0014	Update of sections 5.2 and 4.6 of the SmPC. The Package Leaflet (PL) is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	16/12/2014	SmPC and PL	Sections 4.6 and 5.2 of the SmPC were updated further to kinetic data published in literature in order to update the half-life of methylthioninium chloride and time for discontinuation of breastfeeding. The Package Leaflet was updated accordingly.
IAIN/0018	A.1 - Administrative change - Change in the name and/or address of the MAH	04/08/2014	16/12/2014	SmPC, Labelling and PL	
IAIN/0016/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the PhV system	01/08/2014	n/a		
PSUSA/2029/ 201311	Periodic Safety Update EU Single assessment - methylthioninium chloride	10/07/2014	n/a		PRAC Recommendation - maintenance
IAIN/0012/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a	12/03/2014	n/a		

	starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the PhV system				
IAIN/0011	A.1 - Administrative change - Change in the name and/or address of the MAH	17/01/2014	16/12/2014	SmPC, Labelling and PL	
IB/0008/G	This was an application for a group of variations. 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 B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS	17/12/2013	n/a		
PSUSA/2029/ 201305	Periodic Safety Update EU Single assessment - methylthioninium chloride	05/12/2013	n/a		PRAC Recommendation - maintenance

IB/0007/G	This was an application for a group of variations. B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	26/11/2013	16/12/2014	SmPC, Labelling and PL	
IAIN/0009/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the PhV system	12/11/2013	n/a		

N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/10/2013	16/12/2014	PL	
N/0005	Update the contact details for the MAH local representatives in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/12/2012	16/12/2014	PL	
IB/0004/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	05/07/2012	30/08/2012	Annex II, Labelling and PL	

	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 currently approved batch size B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				

IB/0003	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	12/01/2012	30/08/2012	SmPC and PL	
IAIN/0002/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities	10/01/2012	n/a		
N/0001	The MAH applied to add the list of local representatives in the Package Leaflet. Additionally, the MAH took this opportunity to introduce some minor linguistic corrections to BG, CS, DA, EL, EN, ES, ET, FI, HU, IT, LT, LV, MT, NL, PL, RO, SK, SL, SV, IS and NO Annex III A and B. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/09/2011	30/08/2012	Labelling and PL	