EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Busilvex

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
IA/0036/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	24/06/2022	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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	finished product, including quality control sites (excluding manufacturer for batch release)				
IAIN/0035/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	01/02/2022		SmPC, Annex II, Labelling and PL	
IA/0034/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	17/06/2021	n/a		
IAIN/0033	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	22/12/2020	19/10/2021	Annex II and PL	
II/0031	Update of section 4.5 of the SmPC regarding the interaction with deferasirox and iron chelating agents. The patient leaflet is updated accordingly. Update of the SmPC section 5.2 with minor changes in the paediatric population PK parameters.	01/10/2020	19/10/2021	SmPC, Annex II and PL	SmPC new text Section 4.5 (…) Increases in busulfan exposure have been observed at concomitant administration of busulfan and deferasirox.

	In addition, the MAH took the opportunity to clarify statement on incompatibilities in sections 6.2 and 6.6 and to expand the incompatibility of the polycarbonates syringes with Busilvex to the incompatibility of any infusion components containing polycarbonate with Busilvex. This change has been reflected on the subsection "Instructions for use" of the section 2 "recommendations for safe handling" in the preparation guide of the Package Leaflet. In addition, QRD-related changes have been implemented in annex II. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				The mechanism behind the interaction is not fully elucidated. It is recommended to regularly monitor busulfan plasma concentrations and, if necessary, adjust the busulfan dose in patients who are or have recently been treated with deferasirox. (…) Package Leaflet 2 – What you need to know before you take Busilvex (…) Other medicines and Busilvex (…) Particular caution should be taken if you use itraconazole and metronidazole (used for certain types of infections), or ketobemidone (used to treat pain) or deferasirox (a medicine used to remove excess iron from your body), because this may increase the side-effects. (…) For more information, please refer to the Summary of Product Characteristics. 5.2 Pharmacokinetic properties […] Paediatric population A continuous variation of clearance ranging from 2.52 to 3.97 ml/minute/kg has been established in children from < 6 months up to 17 years old. The terminal half-life ranged from 2.24 to 2.5h. […]
IA/0032	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	14/09/2020	n/a		

II/0030/G	This was an application for a group of variations. 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.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	04/07/2019	n/a		
IB/0029/G	This was an application for a group of variations. 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 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	07/01/2019	n/a		
IA/0028	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	14/12/2018	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
PSUSA/464/201607	Periodic Safety Update EU Single assessment - busulfan	23/03/2017	24/05/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/464/201607.
IB/0026	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/09/2016	n/a		
IA/0025	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	31/03/2016	n/a		
IAIN/0023	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	04/02/2015	n/a		
IA/0022/G	This was an application for a group of variations. 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 A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	04/12/2014	n/a		

II/0019	Extension of indication for Busilvex following fludarabine (FB) as conditioning treatment prior to haematopoietic progenitor cell transplantation (HPCT) in adult patients who are candidates for a reduced-intensity conditioning (RIC) regimen. Consequently, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC and the package leaflet are updated. The MAH also took the opportunity to update the product information in line with QRD template version 9.0. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/07/2014	26/08/2014	SmPC, Labelling and PL	Please refer to the assessment report: Busivex-H-472-VAR-II-19-en.
PSUSA/464/201307	Periodic Safety Update EU Single assessment - busulfan	20/03/2014	22/05/2014		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/464/201307.
IB/0020	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)	06/12/2013	22/05/2014	SmPC	
IA/0018	A.7 - Administrative change - Deletion of manufacturing sites	11/02/2013	n/a		
IB/0017	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	13/11/2012	29/11/2013	SmPC and PL	To update section 4.8 of the SmPC including the ADR "hypogonadism" with a frequency not known and amend section 4 of the Package leaflet accordingly and to make minor editorial changes in PI.

IA/0016/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	23/07/2012	n/a		
II/0015	Update of SmPC section 4.8 and section 4 of the Package leaflet in order to include the ADRs "premature menopause" and "ovarian failure" with a frequqency "not known" as requested by CHMP with assessment of FUM029. In addition, the frequency for the ADRs "cataract", "corneal thinning" and "lens disorders" reported with oral busulfan was clarified with "not known" in SmPC section 4.8 as well as section 4 of the Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	21/06/2012	20/07/2012	SmPC and PL	The ADRs "premature menopause" and "ovarian failure have been added in the table of ADRs in section 4.8 with a frequency "not known. In addition, the frequency for the ADRs "cataract", "corneal thinning" and "lens disorders" reported with oral busulfan was clarified with "not known" in SmPC section 4.8 . Section 4 of the package leaflet has been updated with information regarding lens disorders including clouding of the lens of the eye (cataract), and blurred vision (corneal thinning) as well as menopausal symptoms and female infertility with a frequency of "not known".
II/0014	Update of SmPC sections 4.4 and 5.2 in order to include information related to the drug monitoring for dose-adjustment in infants < 9 kg as requested by CHMP with assessment of FU2 19.5 and FU2 20.5. In addition, the MAH took the opportunity to update	21/06/2012	20/07/2012	SmPC, Annex II, Labelling and PL	In children < 9 kg, a therapeutic drug monitoring may be justified on a case by case basis, in particular in extremely young children and neonates. A population pharmacokinetic analysis has been performed in a cohort of 205 children adequately distributed with

	the PI in line with the latest QRD template version. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				respect to bodyweight (3.5 to 62.5 kg), biological and diseases (malignant and non-malignant) characteristics, thus representative of the high heterogeneity of children undergoing HPCT. This study demonstrated that bodyweight was the predominant covariate to explain the busulfan pharmacokinetic variability in children over body surface area or age. The recommended posology for children enabled over 70% up to 90% of children ≥ 9 kg in achieving the therapeutic window (900-1500 µmol/L.minute). However a higher variability was observed in children < 9 kg leading to 60% of children achieving the therapeutic window (900 1500 µmol/L.minute). For the 40% of children < 9 kg outside the target, the AUC was evenly distributed either below or above the targeted limits; i.e. 20% each < 900 and > 1500 µmol/L.min following 1 mg/kg. In this regard, for children < 9 kg, a monitoring of the plasma concentrations of busulfan (therapeutic drug monitoring) for dose-adjustment may improve the busulfan targeting performance, especially in extremely young children and neonates.
A20/0013	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 17 November 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the Ben Venue Laboratories (BVL) manufacturing site located in Bedford, Ohio (USA).	16/02/2012	25/05/2012		Please refer to the assessment report: EMEA/H/C/00472/A-20/0013

II/0011	Update of SmPC sections 4.2, 4.4 and 4.5 regarding information on seizure prophylaxis treatment based on the results of a Phase II study which was previously assessed with FU2 007.1. The MAH took also the opportunity to update the Product Information in accordance with the latest QRD template. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/06/2011	26/07/2011	SmPC, Annex II and PL	The concomitant systemic administration of phenytoin to patients receiving high dose of oral busulfan has been reported to increase busulfan clearance, due to induction of glutathion-S-transferase whereas no interaction has been reported when benzodiazepines such as diazepam, clonazepam or lorazepam have been used to prevent seizures with high-dose busulfan. No evidence of an induction effect of phenytoin has been seen on Busilvex data. A phase II clinical trial was performed to evaluate the influence of seizure prophylaxis treatment on intravenous busulfan pharmacokinetics. In this study, 24 adult patients received clonazepam (0.025 0.03 mg/kg/day as IV continuous infusions) as anticonvulsant therapy and the PK data of these patients were compared to historical data collected in patients treated with phenytoin. The analysis of data through a population pharmacokinetic method indicated no difference on intravenous busulfan clearance between phenytoin and clonazepam based therapy and therefore similar busulfan plasma exposures were achieved whatever the type of seizure prophylaxis.
IB/0012/G	This was an application for a group of variations. 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	06/06/2011	n/a		

	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation				
IB/0010	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	30/05/2011	n/a	SmPC and PL	Update of SmPC setion 4.8 with the ADR "hepatic veno occlusive disease" following CHMP request with assessment of PSUR 7. The Package Leaflet has been updated accordingly.
R/0009	Renewal of the marketing authorisation.	24/04/2008	08/07/2008	SmPC, Annex II, Labelling and PL	The Marketing Authorisation Holder for Busilvex, Pierre Fabre Médicament, submitted to the EMEA on 21 January 2008 an application for renewal of the Marketing Authorisation for Busilvex. After the assessment of the data provided, the CHMP concluded that " All the relevant sites of manufacture and testing are undergoing regular GMP inspections by an EEA competent authority or MRA partner authority and satisfactory GMP compliance of these sites has been confirmed by the MAH by submission of the appropriate documentation. Appropriate declarations have been submitted concerning the GMP compliance status of the active substance manufacturer. The quality of this product continues to be considered acceptable. " The efficacy of Busilvex during the past years confirm the initial results of the studies submitted at the time of its marketing authorisation; therefore, Busilvex continues to be of clinical benefit to patients with diseases within the approved indications. " The evaluation of the submitted bridging report of the periodic safety updates covering 4 years from 9 July

					2003- 8 July 2007 and 4 month line-listing covering up to 8 November 2007 does not raise any major safety concern. The renewal of the MA of Busilvex has been granted with unlimited validity.
II/0008	New presentation(s)	18/10/2007	04/12/2007	SmPC, Labelling and PL	This variation concerned a change of the container closure system for Busilvex from ampoules to vials, as requested by CHMP. The allowed transition period, during which time both ampoule and vial presentations may be on the market, will come to an end in August 2008. In addition, amendments to the SPC, Annex II, Labelling and Package Leaflet were implemented in several sections, according to the latest QRD templates in order to make the original meaning clearer to users.
IB/0007	IB_42_b_Change in storage conditions of the finished/diluted/reconstituted product	17/04/2007	n/a	SmPC	
IB/0006	IB_37_a_Change in the specification of the finished product - tightening of specification limits	17/04/2007	n/a		
II/0004	Busilvex followed by cyclophosphamide (BuCy4) or melphalan (BuMel) for the conditioning treatment of paediatric patients prior to conventional haematopoietic progenitor cell transplantation. Extension of Indication	15/09/2005	27/10/2005	SmPC and PL	Please refer to the Scientific discussion: Busilvex-H-472-II-04
IA/0005	IA_08_a_Change in BR/QC testing - repl./add. of	04/07/2005	n/a		

	batch control/testing site				
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/08/2004	n/a	PL	
IB/0003	IB_10_Minor change in the manufacturing process of the active substance	20/07/2004	n/a		
I/0001	16_Change in the batch size of finished product	22/10/2003	n/a		