DuoTrav

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
IAIN/0063/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.2.c.1 - Change to importer, batch release	24/09/2021		Annex II and PL	

[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).

	arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
IA/0062	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	24/08/2021	n/a		
IB/0061	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	24/06/2021	n/a		
IA/0060	B.II.c.4.a - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient - Minor change	17/03/2021	n/a		
IB/0058/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	09/10/2020		SmPC, Annex II and PL	

PSUSA/2962/202002	Periodic Safety Update EU Single assessment - timolol / travoprost	01/10/2020	n/a		PRAC Recommendation - maintenance
IAIN/0059/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	30/09/2020	n/a		
IB/0056/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	16/04/2020	n/a		
IA/0055	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	29/05/2019	n/a		
IA/0054	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	05/12/2018	n/a		
T/0053	Transfer of Marketing Authorisation	16/04/2018	31/05/2018	SmPC,	

				Labelling and PL	
II/0052	Update of sections 4.8 of the SmPC in order to add "lid sulcus deepened" and "iris hyperpigmentation" as new adverse drug reactions with frequency not known and to upgrade the frequency of "skin hyperpigmentation (periocular)" from rare to uncommon based on the post-approval review of the safety data. In addition, section 4.8 of SmPC has been updated to align Adverse Drug Reactions table for the travoprost monotherapy. Based on the same safety review, section 4.6 of SmPC has been modified. In addition, the MAH took the opportunity to align the Product information with the currently approved travoprost EU SmPC and QRD version 10 and to update the list of local representatives. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/02/2018	31/05/2018	SmPC, Annex II, Labelling and PL	Following the cumulative review of relevant scientific and accumulated safety information, review of historical study reports and literature the section 4.8 is being updated to: - Add "lid sulcus deepened" and "iris hyperpigmentation" as new ADRs observed in post-marketing setting in section 4.8 with frequency "not known". - Change the frequency category of "skin hyperpigmentation (periocular)" to uncommon, which was previously included as rare. - Update travoprost monocomponent ADRs table in section 4.8 in accordance with the current safety profile of Travatan (travoprost). Additionally, to avoid duplication, adverse reactions already listed within the combination therapy table were removed from the respective monocomponent tables. The Package Leaflet (PL) is updated accordingly.
II/0051	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	23/11/2017	n/a		
PSUSA/2962/ 201702	Periodic Safety Update EU Single assessment - timolol / travoprost	28/09/2017	n/a		PRAC Recommendation - maintenance
T/0049	Transfer of Marketing Authorisation	06/04/2017	16/05/2017	SmPC, Labelling and	

				PL	
IB/0048/G	This was an application for a group of variations. 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.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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.II.c.4.a - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient - Minor change	01/03/2017	n/a		
IB/0047	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	21/02/2017	n/a		
IA/0046	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph.	03/08/2016	n/a		

	Eur. Monograph - Updated certificate from an already approved manufacturer				
II/0044	To include an alternative immediate packaging material for bottles and plugs. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	22/01/2015	19/06/2015	SmPC, Labelling and PL	To include an alternative immedite packaging material of bottles and plugs.
IAIN/0045/G	This was an application for a group of variations. 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 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	21/01/2015	19/06/2015	SmPC, Labelling and PL	
PSUV/0042	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IB/0043	B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	17/09/2014	19/06/2015	SmPC, Labelling and PL	
IB/0039/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	13/08/2014	n/a		

	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.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
IA/0041	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	07/08/2014	n/a		
IG/0452	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	28/07/2014	n/a		
IB/0037	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	13/06/2014	19/06/2015	SmPC, Labelling and PL	
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/01/2014	21/03/2014	PL	
IB/0035	B.I.d.1.a.4 - Stability of AS - Change in the re-test	17/10/2013	n/a		

	period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
IAIN/0034	B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	23/08/2013	n/a		
II/0031	Update of sections 4.2, 4.4, 4.6, 4.7, 4.8 and 4.9 of the SmPC in order to update the safety information in line with the latest Company Core Safety Information (CCSI) document. The Package Leaflet was updated accordingly. Furthermore, the PI was brought in line with the latest QRD template version 9.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	21/03/2014	SmPC, Annex II, Labelling and PL	To reflect reviews mainly based on data from clinical trials and post-marketing experience carried out by the MAH, a safety update of the Product Information for DuoTrav was implemented. In particular, the MAH undertook a review of the adverse drug reactions (ADRs) received from clinical trials and spontaneous post-marketing data up to December 2012. Nineteen clinical trials with DuoTrav Ophthalmic Solution (Travoprost 0.004%/Timolol 0.5% Ophthalmic Solution) were identified. These 19 studies included DuoTrav preserved with benzalkonium chloride (DuoTrav BAK) or DuoTrav preserved with POLYQUAD (DuoTrav PQ or APS). Six of these studies were included in the Initial Marketing Authorisation Application (completed for DuoTrav in 2006, on 721 patients) and thirteen additional studies were completed subsequently (on 1449 patients). Thus, in the pooled studies, a total of 2170 patients had exposure to DuoTrav Ophthalmic Solution. This number enabled calculation of adverse events frequency for a number of events. Additionally, 5 new terms (eye irritation, dysphonia, hypertrichosis, trichiasis, distichiasis) were added to the safety information, based on analyses of these data from

					clinical studies. Three new terms (palpitations, oedema peripheral, dysgeusia) were also added to the safety information, based on review of post-marketing data. The CHMP considered the proposals for the SmPC and the PL to be acceptable and overall improve the text of the prescribing and patient information.
IG/0324	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/07/2013	n/a		
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/07/2013	21/03/2014	PL	
IG/0274	A.1 - Administrative change - Change in the name and/or address of the MAH	19/03/2013	21/03/2014	SmPC, Labelling and PL	
IG/0149/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.h - 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 pharmacovigilance system	06/03/2012	06/03/2012	Annex II	
IB/0026	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	17/02/2012	08/10/2012	SmPC and PL	The essential safety information detailed in the Pharmacovigilance Working Party (PhVWP) recommendations for Duotrav which resulted from a class review of systemic effects of ophthalmic beta-blockers have been adopted and are reflected in the revised SmPC and

					package leaflet (PL).
IG/0107/G	This was an application for a group of variations. C.I.9.h - 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 pharmacovigilance system C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of 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	19/09/2011	n/a		
IG/0072	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	07/06/2011	n/a		
II/0019/G	This was an application for a group of variations. To change the preservative in the finished product. To introduce manufacturing overage for the active substance. To add a new test method in the finished product specification. To change the release and shelf-life specification of the finished product.	17/02/2011	24/03/2011	SmPC, Labelling and PL	

	B.II.a.3.b.2 - Changes in the composition (excipients) of the finished product - Other excipients - Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the product B.II.b.3.e - Change in the manufacturing process of the finished product - Introduction or increase in the overage that is used for the AS B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter as a result of a safety or quality issue B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
IA/0020	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/03/2011	n/a		
IG/0039	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	17/01/2011	n/a	Annex II	
R/0018	Renewal of the marketing authorisation.	22/07/2010	07/10/2010	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of DuoTrav continues to be adequately and sufficiently

					demonstrated and therefore considered that the benefit risk profile of DuoTrav continues to be favourable. The CHMP was of the opinion that the renewal could be granted with unlimited validity. The renewal required amendments to the terms of the Community Marketing Authorisation. The following annexes have been amended: I, II, IIIA and IIIB.
IG/0019	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	14/09/2010	n/a		
IB/0017	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	07/04/2010	n/a		
II/0016	Change(s) to the manufacturing process for the active substance	17/12/2009	08/01/2010		
IB/0015	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	20/02/2009	n/a		
IB/0014	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	20/02/2009	n/a		
II/0012	Update of section 4.8 of the Summary of Product Characteristics following the CHMP recommendation after assessment of the 4th Periodic Safety Update Report. Relevant sections of the Package Leaflet were	18/12/2008	02/02/2009	SmPC and PL	Following assessment of the 4th PSUR for DuoTrav eye drops, the CHMP requested amendments to the SPC, in order to include: - Keratitis,

	amended accordingly. In addition, the MAH took the opportunity to update the contact details of the Estonian, Greek, Hungarian, Latvian, Norwegian, Portuguese, Romanian and Slovenian local representatives in the PL. Update of Summary of Product Characteristics and Package Leaflet				- Corneal erosion, as uncommon ocular ADRs in section 4.8 of the SPC, and to change the category of frequency of arrhythmia from unknown to uncommon.
IA/0011	The MAH has applied for a change of name for the active substance manufacturer. IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	06/10/2008	n/a		
IB/0010	IB_36_a_Change in shape or dimensions of the container/closure - sterile ph. forms/biologicals	23/09/2008	n/a		
II/0009	Further to the CHMP conclusions after assessment of PSUR 3, updates of sections 4.4 (Special warnings and precautions for use), 4.6 (Pregnancy and lactation) and 4.8 (Undesirable effects) of the Summary of Product Characteristics (SPC) and the corresponding changes to sections 2 and 4 of the Package Leaflet (PL) have been carried out. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	31/07/2008	SmPC and PL	Following assessment of the 3rd PSUR for DuoTrav eye drops, the CHMP requested amendments to the SPC. Namely: - Include warnings related to benzalkonium chloride and corneal toxicity in section 4.4; - Include precautions statements in section 4.4 regarding cutaneous absorption of travoprost in pregnant women or women attempting to become pregnant; - Reword section 4.6 to include a statement on harmful effects of travoprost use during pregnancy (consistently with safety data for travoprost-containing products); and

					- As 'asthma' has been actually reported as a respiratory disorder with Duotrav use, it should appear as such in section 4.8 (being relocated from the current section 'adverse events that have been seen with one of the components and may potentially occur with DuoTrav'. With this variation the MAH fulfilled the above requests. As other adverse reactions were also reported in PSURs to have been observed with Duotrav, consistently with the relocation of 'asthma' described above, the MAH made further changes to section 4.8 of the SPC. A number of other adverse reactions were relocated within the section, as they were observed during DuoTrav use. Namely: - 'Cardiac failure', 'cerebrovascular accident', 'syncope', 'paraesthesia', 'alopecia', 'chest pain' and 'depression'. Additionally, - 'Tachycardia', for which cases were reported in the 3rd PSUR, was included in section 4.8 of the SPC. - Section 4.8 of the SPC was modified to reflect the fact that the event 'iritis' had recently been reported during DuoTrav use. The corresponding changes to the PL were also implemented.
II/0008	Amendment of section 4.8 of the Summary of Product Characteristics (SPC) to replace some wording, as requested by the CHMP following assessment of the 2nd PSUR. Additional minor changes to section 4.8 have been made to reflect latest guidelines. Section 4	21/02/2008	31/03/2008	SmPC, Labelling and PL	Following assessment of the 2nd Periodic Safety Update Report (PSUR) for DuoTrav eye drops, the CHMP recommended amendments to section 4.8 of the SPC. In particular, in order to make its section 4.8 as clear as possible to prescribers, the deletion of the following

	of the Package Leaflet (PL) has been amended accordingly. Update of Summary of Product Characteristics, Labelling and Package Leaflet				paragraph was requested: "Travoprost: Additional undesirable treatment-related effects reported in clinical trials with concomitant therapy (travoprost and timolol) or with monotherapy with travoprost, or post-marketing events reported in the SPC for travoprost that have not been reported with DuoTrav include the following presented in decreasing order of seriousness within each SOC (body system):" as well as the analogue paragraph applicable to timolol. These paragraphs were replaced with the sentence: "Additional adverse events that have been seen with one of the components and may potentially occur with DuoTrav". Additionally, 'macular oedema', 'corneal disorders', 'conjunctivitis', 'eyelid ptosis', 'rash' and 'arrhythmia' were moved from the sections on individual active ingredients, as applicable, to include them under the list of adverse reactions observed with DuoTrav use during post-marketing experience. The PL was updated according to the above changes.
II/0007	Change(s) to the manufacturing process for the finished product	21/02/2008	31/03/2008	PL	
IB/0006	IB_10_Minor change in the manufacturing process of the active substance	12/12/2007	n/a		

II/0005	Quality changes	19/07/2007	08/08/2007		
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/02/2007	n/a	PL	
IB/0003	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	05/12/2006	n/a		
IB/0002	IB_12_b_01_Change in spec. of active subst./agent in manuf. of active subst. - test parameter AS	16/08/2006	n/a		