Toviaz

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/0069/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished	20/11/2023	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).

	product - Minor changes to an approved test procedure				
II/0068	Update of section 4.4 of the SmPC to amend an existing warning on angioedema and 4.8 of the SmPC in order to add hypoaesthesia oral to the list of adverse drug reactions (ADRs) with a frequency rare based on a cumulative review of safety database cases and literature. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with the QRD template v10.3. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/10/2023		SmPC and PL	Based on cumulative reviews, the warning in section 4.4 of SmPC on angioedema has been updated to reflect that 'some cases may be associated with upper airway swelling and may be life-threatening'. In addition, hypoaesthesia oral had been added in section 4.8 of SmPC with a frequency 'rare'. For more information, please refer to the Summary of Product Characteristics.
IA/0067	A.7 - Administrative change - Deletion of manufacturing sites	10/01/2023	15/09/2023	Annex II and PL	
II/0063	C.I.3 Update of sections 4.2, 5.1 and 5.2 of the SmPC with the results from study A0221047, to evaluate the safety and efficacy of fesoterodine in subjects aged 6 to 17 years with neurogenic detrusor overactivity. The change was suggested in the outcome of the EMEA/H/C/000723/P46/030.1. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet	06/10/2022	15/09/2023	SmPC, Annex II and PL	This variation concerned the submission of data from Study A0221047, a phase 3, randomized, open-label study to evaluate the safety and efficacy of fesoterodine on paediatric patients aged 6 to 17 with symptoms of detrusor overactivity associated with Neurogenic Detrusor Overactivity (NDO). Treatment with fesoterodine 4 mg or 8 mg tablets resulted in improvements from baseline in maximum cystometric bladder capacity (MCBC) at Week 12 for paediatric patients > 25 kg, with numerically higher changes from baseline for

	and to bring the PI in line with the latest QRD template version 10.1. C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH				fesoterodine 8 mg tablets than for fesoterodine 4 mg tablets. Overall, the safety profile in paediatric patients with neurogenic detrusor overactivity was similar to that observed in adults with overactive bladder syndrome. These safety and efficacy data from Study A0221047 have been described in section 5.1 and 5.2. of the SmPC. No recommendation on posology can be made and uncertainties on the long-term safety remain. Overall, data from this study, although considered positive, remain limited. The safety and efficacy of Toviaz in children aged less than 6 years has not been established. For more information, please refer to the Summary of Product Characteristics.
IA/0066	A.7 - Administrative change - Deletion of manufacturing sites	30/08/2022	n/a		
II/0065/G	This was an application for a group of variations. B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	03/03/2022	n/a		

	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product 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.4.c - Change in the batch size (including batch size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product or a new bioequivalence study 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.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 B.II.a.2.b - Change in the shape or dimensions of the pharmaceutical form - Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses A.7 - Administrative change - Deletion of manufacturing sites				
II/0062	Submission of an updated RMP version 10.0 in order to align the important identified risks, important potential risks, and missing information with the new Guideline on good pharmacovigilance practice (GVP) Module V - Risk management systems (Revision 2.0), and to address the PSUR PRAC recommendation (EMEA/H/C/PSUSA/00001387/202004). RMP Version 10.0 is accepted.	28/10/2021	n/a		The current variation involved revision of the list of safety concerns of the Risk Management Plan (RMP) according to the current Guideline on good pharmacovigilance practice (GVP) Module V - Risk management systems (Revision 2.0) and the outcome of the last PSUR PRAC recommendation (EMEA/H/C/PSUSA/00001387/202004). The important identified risks (Urinary retention, Angioedema), important potential risks (QT prolongation, Hepatotoxicity, Cognitive function impairment) and missing information (Elderly male patients, Paediatric patients, Pregnant or nursing women)

	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				were removed from RMP since no additional risk minimisation measures nor additional pharmacovigilance activities are proposed.
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/10/2021	15/09/2023	PL	
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/11/2020	15/09/2023	PL	
PSUSA/1387/ 202004	Periodic Safety Update EU Single assessment - fesoterodine, desfesoterodine	26/11/2020	n/a		PRAC Recommendation - maintenance
IA/0059	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/11/2020	n/a		
N/0057	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/11/2019	16/07/2020	PL	
N/0056	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/09/2019	16/07/2020	Labelling	
IAIN/0055	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	29/07/2019	n/a		
IB/0054/G	This was an application for a group of variations.	22/07/2019	16/07/2020	SmPC,	

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.z - Change in the specification parameters and/or limits 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)			Labelling and PL	
IA/0053	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	19/12/2018	n/a		
T/0052	Transfer of Marketing Authorisation	11/07/2018	30/07/2018	SmPC, Labelling and PL	

IB/0051	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	22/03/2018	n/a		
PSUSA/1387/ 201704	Periodic Safety Update EU Single assessment - fesoterodine, desfesoterodine	30/11/2017	n/a		PRAC Recommendation - maintenance
II/0049	Update of the SmPC sections 4.6 and 5.3 with revised information from reproductive toxicity studies in mice. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.0. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/09/2017	30/07/2018	SmPC and Labelling	In this variation the MAH has revised the product information to reflect that a study of fertility and early embryonic development in mice, showed some findings, namely a lower number of corpora lutea, implantation sites, and viable foetuses in females administered fesoterodine at 45 mg/kg/day for 2 weeks prior to mating and continuing through day 7 of gestation. Findings in mice corresponded to exposures approximately 5 to 19 times those at the maximum recommended human dose (MRHD) on female fertility and 6 times those at MRHD on fetotoxicity, however, the clinical implications of these animal findings are not known.
IA/0048	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	18/10/2016	n/a		
IB/0047	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/08/2016	06/07/2017	SmPC, Annex II and PL	
N/0046	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	23/09/2015	PL	
PSUV/0042	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance

IAIN/0045	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	23/10/2014	23/09/2015	Annex II and PL	
IA/0044	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	25/09/2014	n/a		
IA/0043	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	21/08/2014	n/a		
IB/0041	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	01/07/2013	n/a		
IG/0235/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.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
IAIN/0039/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	28/09/2012	25/10/2012	SmPC, Labelling and PL	

	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				
IG/0169/G	This was an application for a group of variations. 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.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	08/06/2012	n/a		
R/0034	Renewal of the marketing authorisation.	19/01/2012	15/03/2012		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 Toviaz continues to be favorable. The CHMP was of the opinion that the renewal could be granted with unlimited validity. However the MAH will continue to submit yearly PSURs, unless otherwise specified by the CHMP.
II/0033	Update of Summary of Product Characteristics and Package Leaflet. Changes to section 4.4 of the SmPC to include a warning regarding the risk of angioedema. The Package Leaflet has been updated accordingly.	22/09/2011	24/10/2011	SmPC and PL	Review of the available data from the clinical trials and post-marketing reports, conducted by the MAH, concluded that cases of angioedema have been reported, in some cases shortly after initiation of the treatment with fesoterodine. Since angioedema can cause potentially

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				serious medical consequences the MAH proposed to include a warning to stop the treatment with fesoterodine in case an angioedema develops. This was endorsed by the CHMP.
IA/0035	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	27/09/2011	n/a		
II/0029	Update to sections 4.2, 4.5 and 4.8 of the SmPC with safety data regarding confusional state, palpitations, blurred vision and angioedema, as well as clinical study results for a study evaluating the effect of fluconazole on fesoterodine, in accordance with the request from the CHMP following the assessment of PSUR 5. Sections 2 and 4 of the PIL were updated accordingly. Additionally, the MAH took this oportunity to make some editorial amendments in sections 4.5 and 10 of the SmPC and section 6 of the PIL. Finally, the data presentation in section 4.8 of the SmPC has been revised in line with the Guideline on the Summary of Product Characteristics. 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	17/02/2011	24/03/2011	SmPC and PL	Results of study A0221080, which evaluated the effect of fluconazole, a moderate CYP3A4 inhibitor, on the single-dose pharmacokinetics of fesoterodine in healthy subjects, showed that co-administration of fesoterodine 8 mg with fluconazole 200 mg BID increased the Cmax and AUCinf of 5-HMT by approximately 19% and 27%, respectively. Section 4.5 of the SmPC was updated to reflect this information, and a related change was introduced in SmPC section 4.2 regarding the concomitant administration of moderate CYP3A4 inhibitors. Additionally, further to reports included in the 5th PSUR (covering the period 20.04.09 - 19.10.09), the following undesirable effects were included in section 4.8 of the SmPC: palpitations (uncommon), blurred vision (uncommon), angioedema (rare) and confusional state (rare).

IG/0044/G	This was an application for a group of variations. 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 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	02/03/2011	n/a	Annex II	
IB/0032	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	14/01/2011	n/a	SmPC, Annex II and PL	Implementation of changes to Section 4.8 to add "pruritus" and "urticaria" as adverse events reported post-marketing as requested in PSUR 6 AR. The MAH also takes the opportunity to update the PIL with an administrative change for the Icelandic local representative and to make other editorial changes in some of the EU language translations.
II/0031	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	25/10/2010	SmPC	The MAH has proposed change to section 4.5 of the SmPC with information on interaction with warfarin from a clinical study in healthy volunteers to evaluate the steady-state effect of fesoterodine (8 mg once daily) on the PK and PD of a single dose of warfarin (25 mg). From this study it was concluded that their was a lack of interactive PK effect or interactive PD effect when warfarin is co-administered with fesoterodine. These results are in line with theoretical

					considerations concerning warfarin metabolism, as well as the conclusion from the review of the safety database. The update of section 4.5 of the SmPC is acceptable and does not affect the overall positive benefit-risk balance of this product.
IA/0030/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	25/06/2010	n/a		
II/0025	Update to sections 4.4 and 4.8 of SmPC with information on urinary retention as well as gastroesophageal reflux. The Package Leaflet was updated accordingly in sections 2 and 4. This update was made further to the request of the CHMP following assessment of 4th PSUR (period 20.10.2008 - 19.04.2009). Update of Summary of Product Characteristics and Package Leaflet	22/04/2010	04/06/2010	SmPC and PL	The MAH has reviewed the safety data from eight double-blind, placebo-controlled fesoterodine clinical trials, which included 2,349 subjects that received placebo and 3,791 subjects that received fesoterodine, from four open-label studies and from the MAH's safety database (from 20 April 2007 through 19 October 2009) . The incidence rate for urinary retention in the pooled double-blind trials was observed to be 0.7% for fesoteridine and 0.1% for placebo. Taking also into account the open label studies, the pooled incidence rate in fesoteridine

					treated patients in clinical trials is 0.9%. The search of the safety database confirmed 38 cases of urinary retention considered as serious (i.e. associated with catherisation and/or hospitalization). Many of these cases were reported in elderly male patients, who had a history consistent with benign prostatic hyperplasia. It is therefore considered appropriate to indicate 'clinically significant prostate enlargement due to benign prostatic hyperplasia' as an example of a condition with clinically significant bladder outflow obstruction at risk of urinary retention. Additionally, it was also concluded from the same pooled data, that gastroesophageal reflux, whose incidence rate was observed to be 0.4%, should be added as an adverse drug reaction. The search in the safety database confirmed 4 cases where 3 of the 4 cases provided very little information. The remaining case involved a 70-year-old male patient who experienced acid reflux during the first week of starting fesoterodine 8 mg daily. The frequency of gastroesophageal reflux is considered as 'uncommon'.
IB/0027	To add Near Infrared Spectroscopy (NIR) as an alternate method for water content determination in the finished product B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	04/03/2010	n/a		
II/0024	Addition of alternative manufacturing process for an intermediate in the synthesis of fesoterodine fumarate and addition of an alternate test side.	17/12/2009	06/01/2010		

	Change(s) to the manufacturing process for the active substance				
II/0021	Update of DDPS (Pharmacovigilance)	25/06/2009	29/07/2009	Annex II	
IB/0023	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	08/07/2009	08/07/2009	SmPC, Labelling and PL	
IB/0022	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	08/07/2009	08/07/2009	SmPC, Labelling and PL	
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/02/2009	n/a	PL	
IA/0020	IA_36_ b_Change in shape or dimensions of the container/closure - other pharm. forms	04/02/2009	n/a		
II/0017	Update of the Detailed Description of the Pharmacovigilance system (DDPS) version 1.1. Update of DDPS (Pharmacovigilance)	23/10/2008	28/11/2008	Annex II	
II/0016	The applicant has applied to add 50 cc and 100 cc white opaque High-Density Polyethylene Bottles as an alternate primary packaging for Toviaz 4 mg and 8 mg prolonged release tablets. The new pack sizes to be included are 30 tablets (50 cc bottle) and 90 tablets (100 cc).	23/10/2008	28/11/2008	SmPC, Labelling and PL	

	New presentation(s)				
II/0015	The MAH applied for the addition an alternative manufacturer for the active substance. In this context, the MAH introduced minor changes to the manufacturing process. Update of or change(s) to the pharmaceutical documentation	23/10/2008	28/10/2008		
IA/0018	IA_05_Change in the name and/or address of a manufacturer of the finished product	09/09/2008	n/a	Annex II and PL	
II/0014	Change(s) to shelf-life or storage conditions	30/05/2008	07/07/2008	SmPC, Labelling and PL	
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/05/2008	n/a	Labelling and PL	
II/0009	Change(s) to the manufacturing process for the active substance	19/03/2008	31/03/2008		
II/0008	Change(s) to the manufacturing process for the active substance	19/03/2008	31/03/2008		
IA/0011	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	01/02/2008	01/02/2008	SmPC, Labelling and PL	
IA/0010	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	01/02/2008	01/02/2008	SmPC, Labelling and	

				PL	
IA/0007	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	18/12/2007	n/a	Annex II and PL	
IA/0005	IA_39_Change/addition of imprints, bossing or other markings	18/12/2007	n/a	SmPC and PL	
IA/0006	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	14/12/2007	n/a		
IB/0002	IB_12_b_01_Change in spec. of active subst./agent in manuf. of active subst. - test parameter AS	29/11/2007	n/a		
IB/0004	IB_12_b_01_Change in spec. of active subst./agent in manuf. of active subst. - test parameter AS	16/10/2007	n/a		
IB/0003	IB_12_b_01_Change in spec. of active subst./agent in manuf. of active subst. - test parameter AS	16/10/2007	n/a		
T/0001	Transfer of Marketing Authorisation	08/08/2007	18/09/2007	SmPC, Labelling and PL	