Dynastat

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
N/0091	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/06/2024		PL	
IB/0092	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/05/2024		SmPC 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).

PSUSA/2314/202303	Periodic Safety Update EU Single assessment - parecoxib	14/12/2023	08/02/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2314/202303.
II/0088	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/01/2024		SmPC and PL	
IAIN/0090/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	03/11/2023	08/02/2024	Annex II and PL	
IB/0089	A.7 - Administrative change - Deletion of manufacturing sites	19/10/2023	n/a		
IA/0086	A.7 - Administrative change - Deletion of manufacturing sites	06/12/2022	n/a		
II/0085	Update of section 4.9 of the SmPC in order to amend it with the current medical guidance for acute NSAIDs poisoning/overdose. In addition, the MAH took the opportunity to introduce a minor editorial change to the PI and to update the list of local representatives in the Package Leaflet.	16/06/2022	20/10/2022	SmPC and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0084	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	26/01/2022	n/a		
IB/0083	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/10/2021	20/10/2022	SmPC	
N/0082	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/09/2021	20/10/2022	PL	
IAIN/0081/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.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	12/02/2021	n/a		
PSUSA/2314/ 202003	Periodic Safety Update EU Single assessment - parecoxib	26/11/2020	n/a		PRAC Recommendation - maintenance
IB/0080	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/10/2020	16/04/2021	SmPC, Labelling and PL	

IB/0079/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	14/08/2020	n/a		

	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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 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 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 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 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 B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-				

	significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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 and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
II/0077	Update of section 4.3 of the SmPC to add reaction with eosinophilia and systemic symptoms syndrome (DRESS syndrome) to the existing contra-indication and section 4.4 of the SmPC to add a warning on possible occurrence of DRESS syndrome with	07/05/2020	16/04/2021	SmPC, Annex II, Labelling and PL	A cumulative review of the clinical trial database and the safety database of the MAH as well as a cumulative review of the literature did not identify DRESS syndrome cases involving parecoxib exposure. However, DRESS syndrome, although a rare event, is identified as a potential risk with

	parecoxib. Editorial changes are made to the product information in line with the QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				parecoxib exposure since DRESS syndrome has been identified with celecoxib (parecoxib has a chemical structure very similar to that of celecoxib) and is a life-threatening condition that may have a fatal outcome if the signs and symptoms are not recognized by a healthcare professionals. Therefore, parecoxib is contra-indicated in patient with history of previous serious allergic drug reaction of any type, especially cutaneous reactions such as drug reaction with eosinophilia and systemic symptoms syndrome (DRESS syndrome). DRESS syndrome may occur with parecoxib exposure based on other serious skin reactions reported with celecoxib and valdecoxib exposure.
N/0076	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/11/2019	01/04/2020	PL	
II/0075	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	04/04/2019	01/04/2020	SmPC, Labelling and PL	
T/0073	Transfer of Marketing Authorisation	24/08/2018	28/09/2018	SmPC, Labelling and PL	
IB/0074	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	19/09/2018	n/a		
II/0072	Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to update the information on the use of parecoxib beyond 3 days based on a recent publication on the 'Safety of parecoxib when used for more than 3 days for the management of	21/06/2018	28/09/2018	SmPC and PL	The SmPC section 4.2 and 4.4 have been updated to add cross-reference to section 5.1. The SmPC section 5.1 has been updated to include data on use of parecoxib beyond 3 days. Overall, the occurrence of

	postoperative pain'; this is an observatory study of the Pfizer clinical trial database to identify randomized, double-blind, placebo controlled trials in which patients could have, potentially, received parecoxib for longer than 3 days for the management of postoperative pain. 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				adverse events in patients receiving parecoxib for 4-7 days (median duration 4 days) was low after treatment Day 3 and similar to placebo. However, as the cardiovascular risk of (COX-2) specific inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose of parecoxib should be used. In addition, Package Leaflet has been updated to include diazepam and omeprazole in a list of medicines that need to be communicated to doctor before taking parecoxib as they may have impact on dosing of Dynastat. This information is already included in SmPC.
IB/0071	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 originally approved batch size	19/12/2017	n/a		
PSUSA/2314/ 201703	Periodic Safety Update EU Single assessment - parecoxib	30/11/2017	n/a		PRAC Recommendation - maintenance
IB/0069/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.1.f - Replacement or addition of a	25/04/2017	n/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.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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 originally approved batch size 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.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
II/0068/G	This was an application for a group of variations. C.I.4 – Update of section 4.4 of the SmPC in order to update the safety information related to alcohol use and gastrointestinal (GI) risk. C.I.4 - Update of section 4.6 of the SmPC in order to update the safety information related to oligohydramnios if the product is used during second or third trimester of pregnancy.	23/02/2017	22/02/2018	SmPC, Annex II, Labelling and PL	4.4 Special warnings and precautions for use Gastrointestinal Upper gastrointestinal (GI) complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with parecoxib. Caution is advised in the treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly, glucocorticoids, selective

	In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, to bring the PI in line with the latest QRD template version 10.0 and to correct some editorial/typographical errors. 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				serotonin reuptake inhibitors, patients ingesting alcohol or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding. 4.6 Fertility, pregnancy and lactation Pregnancy NSAID use during the second or third trimester of pregnancy may cause foetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible. Pregnant women on NSAIDs should be closely monitored for amniotic fluid volume. Dynastat is contraindicated in the third trimester of pregnancy (see section 4.3).
IA/0066	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)	29/06/2016	n/a		
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	15/10/2015	PL	
IAIN/0065	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	29/04/2015	n/a		
II/0063/G	This was an application for a group of variations. Update of SmPC Section 4.4 Special warnings and	18/12/2014	15/10/2015	SmPC and PL	With this variation application, the MAH updated the following drug interactions in Section 4.4 'Special warnings or precautions for use' and Section 4.5 'Interactions with

	precautions for use with information on interaction of NSAIDs with glucocorticoids, with selective serotonin reuptake inhibitors (SSRIs) and with oral anticoagulants. Update of SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction with information on interaction of NSAIDs with antihypertensive drugs (i.e., angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor antagonists [AIIA], diuretics, and beta-blockers), cyclosporine and methotrexate (MTX). 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 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 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				other medicinal products and other forms of interaction' of the parecoxib (Dynastat) Summary of Product Characteristics (SmPC) following the safety review of these drug interactions: • NSAID interaction with antihypertensive drugs (i.e., angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor antagonists [AIIA], diuretics, and betablockers); • NSAID interaction with cyclosporin; • NSAID interaction with methotrexate (MTX); • NSAID interaction with oral anticoagulants; • NSAID interaction with selective serotonin reuptake inhibitors (SSRIs); • NSAID interaction with glucocorticoids.

PSUV/0062	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
II/0061/G	This was an application for a group of variations. Changes to the composition and dimensions of the bromobutyl rubber stopper. 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 B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	25/09/2014	15/10/2015	SmPC and PL	
IB/0059/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.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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	27/01/2014	n/a		

	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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 originally approved batch size 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 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 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 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.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products				
IA/0060	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	29/11/2013	n/a		
IB/0058/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of	06/08/2013	n/a		

	the finished product - Other variation				
IB/0057/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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	29/07/2013	n/a		
II/0055	Update section 4.6 of the Summary of Product Characteristics (SmPC) regarding information on the excretion of parecoxib in human milk. The Package Leaflet was updated accordingly. In addition, an update of the list of local representatives in the Package Leaflet was made and the Product Information was amended in line with the latest QRD template. The patient friendly term 'powder for injection' was also added on the vial labelling and reflected on the section 3 of the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	30/05/2013	03/12/2013	SmPC, Annex II, Labelling and PL	Following newly available data on the literature regarding the transfer of parecoxib and valdecoxib into human milk, the CHMP recommended to revise the information in the SmPC and PL regarding breastfeeding as follows: - SmPC: Administration of a single dose of parecoxib to lactating women following caesarean section resulted in the transfer of a relatively small amount of parecoxib and its active metabolite valdecoxib into human milk, and this resulted in a low relative dose for the infant (approximately 1% of the weight-adjusted maternal dose). Dynastat must not be administered to women who breast-feed (see section 4.3). - PL: If you are breast-feeding, you must not receive Dynastat, as a small amount of Dynastat will be transferred to your breast milk.
II/0052	Update of the SmPC in order to update the safety information related to the risks of miscarriage during the first two trimesters of pregnancy and of	21/03/2013	03/12/2013	SmPC, Annex II and PL	Results from studies and post-marketing suggested a risk for spontaneous abortion and reversible decreased fertility with some anti-inflammatory drugs called NSAIDs, such as

	reversible infertility based on data from published literature. The Package Leaflet was updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				Dynastat. The SmPC for Dynastat already includes a contra-indication for this product during the third trimester of pregnancy and a recommendation against the use of this product during the two first trimesters of pregnancy. The warnings were expanded with the safety information related to these risks, based on the available data. The following text was added to the Package Leaflet for Dynastat: "NSAIDs, including Dynastat, may make it more difficult to become pregnant. You should tell your doctor if you are planning to become pregnant or if you have problems becoming pregnant."
IB/0056	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)	01/03/2013	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).
IB/0053/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	19/11/2012	n/a		

	aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation 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.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.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.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.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				
II/0047	Update of section 4.5 of the SmPC with the safety information pertaining to interaction of NSAIDs with ACE and Angiotensin-II inhibitors. The Package Leaflet is updated accordingly. Minor editorial changes have also been introduced. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	24/10/2012	SmPC, Labelling and PL	With this variation the MAH took the opportunity to update the information on the interactions between anti-inflammatory drugs (Nonsteroidal anti-inflammatory drugs, NSAIDs) including Dynastat and drugs inhibiting the functioning of the hormone, angiotensin, i.e. ACE and Angiotensin-II inhibitors.
IB/0051	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	15/10/2012	n/a		

IB/0050/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites C.I.7.b - Deletion of - a strength A.7 - Administrative change - Deletion of manufacturing sites	18/07/2012	10/10/2012	SmPC, Annex II, Labelling and PL	Deletion of manufacturing sites and deletion of 20 mg product strength and corresponding 1 ml solvent ampoule.
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		
IB/0048/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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	30/05/2012	n/a		

	corresponding test method				
R/0045	Renewal of the marketing authorisation.	17/11/2011	24/01/2012	SmPC, Annex II, Labelling and PL	Parecoxib is indicated in the EU for the short-term treatment of postoperative pain in adults. The efficacy of parecoxib has been established in studies of dental, gynaecologic (hysterectomy), orthopaedic (knee and hip replacement) and coronary artery bypass graft surgical pain. Efficacy data from nine clinical studies conducted since the last renewal indicate that the efficacy of Dynastat remains unchanged. In the decade since the initial authorisation, the use of parecoxib has been associated with unwanted events which were not evident at the time of the marketing approval; the most notable being renal failure, myocardial infarction, and serious skin reactions including Stevens Johnson Syndrome. The safety sections of the product information have been revised accordingly. The off-label use of the product within a non-operative setting has been observed. The company will therefore follow-up on off-label use through pharmacovigilance activities and continue to closely monitor the following events in future PSURs: cardiovascular and cerebrovascular events (thromboembolic and non-thromboembolic), haemorrhage events, and severe skin-related events. Based on the review of the data submitted for the renewal application, the CHMP considers that the benefit-risk balance for parecoxib remains favourable.
II/0046	Addition of warnings on mode of administration and severe hypotension to section 4.4 and the adverse event "circulatory collapse" to section 4.8 of the SmPC with the corresponding update of the patient leaflet.	20/10/2011	22/11/2011	SmPC and PL	In this variation additional information was introduced to the product information for Dynastat to remind doctors and other healthcare professionals who prescribe and use the medicine that Dynastat should only be given as an intravenous or intramuscular injection. Furthermore,

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				prescribers and patients are being informed that Dynastat may cause collapse as a result of lowering blood pressure.
II/0044	This Type II variation updates instructions for healthcare professionals on dosing and administration of Dynastat in the Package Leaflet as requested by CHMP. An additional consequential update to the SmPC is also made to Section 4.2 Posology and method of administration. The wording 'There is limited clinical experience with Dynastat treatment beyond three days' is added to this section. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	23/06/2011	SmPC and PL	As a result of this variation the section of the Package Leaflet dedicated to the Healthcare Professionals was updated with the detailed information on how to dose Dynastat, the recommended duration of treatment and that clinical experience with administering the product beyond 3 days is limited. Consequently, the section 4.2 of the Summary of Product Characteristics was also updated to reflect the limitation in clinical experience when Dynastat is given for more than 3 days.
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)	02/03/2011	n/a		

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0042	Section 4.9 of the SPC has been updated to reflect new data that became available on overdose. In addition the addresses of the local representatives have been updated in the Package Leaflet and the version number of the DDPS was deleted from Annex II.B of the SPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/01/2011	21/02/2011	SmPC, Annex II and PL	Following emerging post authorisation safety data the MAH updated section 4.9. to better reflect the known adverse events in case of overdose.
IA/0043	A.7 - Administrative change - Deletion of manufacturing sites	29/11/2010	n/a		
II/0040	Update of section 4.8 of the SmPC following a safety integrated analysis of placebo-controlled trials conducted in postoperative pain. The Package leaflet is amended accordingly. This variation application is submitted further to the request of the CHMP following assessment of PSUR Nr. 9, covering the period 01 April 2008 through 31 March 2009. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/07/2010	06/09/2010	SmPC, Labelling and PL	Based on a safety integrated analysis of 28 placebo-controlled trials conducted in postoperative pain the MAH updated the section 4.8 of the SmPC. The following events were added to the SmPC anaphylactoid reaction, oedema mouth (perioral swelling), urticaria, rash, injection site pain, injection site reaction, myocardial infarction, pulmonary embolism, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, orthostatic hypotension, constipation, dry mouth, anorexia, gastrooesophageal reflux disease, gastrointestinal sounds abnormal, dizziness, hyperhidrosis, arthralgia, asthenia, hyperglycaemia, ear pain, post procedural complication (skin) oesophagitis and pancreatitis. Most of the events are related ADR to already labelled events in section 4.8 of the SmPC or have a relationship to a concept already covered

					in the warnings section 4.4 or have a relationship to a known class effects. Overall the CHMP concluded that the changes provide additional information and more accurate guidance to prescribers on the safe and effective use of parecoxib.
II/0041	Update of section 4.4 of the SmPC based on the results of a literature review to inform that parecoxib should be used with caution in patients with compromised cardiac function or hypertension as fluid retention and oedema have been observed in patients taking non-steroidal anti-inflammatory drug (NSAID). The Package leaflet (PL) is updated accordingly. In addition the MAH took the opportunity to make a minor editorial change in the SmPC and PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/06/2010	28/07/2010	SmPC and PL	There have been case reports in the literature of patients with a predisposition to sodium retention, in particular because of congestive heart failure (CHF) in which the use of NSAIDs had marked clinical implications. Existing CHF may worsen after use of NSAIDs by inhibition of diuretic therapy and by adverse renal effects, especially in elderly patients with renal impairment and cardiovascular co-morbidity. As with other drugs known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in some patients taking parecoxib. Therefore, parecoxib should be used with caution in patients with compromised cardiac function, pre-existing oedema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia. As with all NSAIDs, parecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. NSAIDs, including parecoxib, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with parecoxib and throughout the course of therapy. Data from the literature show that there is an increased risk of gastrointestinal, cardiovascular, renal and other toxicities associated with use of multiple NSAIDs. The concomitant use of parecoxib with other non-aspirin NSAIDs should

					therefore be avoided.
IA/0039	IA_05_Change in the name and/or address of a manufacturer of the finished product	08/12/2009	n/a	Annex II and PL	
IA/0038	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	08/12/2009	n/a		
II/0036	To update Section 4.4 "Special warnings and precautions for use" of the Summary of Products Characteristics (SPC) on information on reports of fatal skin reactions. Update of Summary of Product Characteristics	25/06/2009	23/07/2009	SmPC	In the 8th Periodic Safety Update Report for parecoxib, 3 cases of fatal skin reactions in connection with parecoxib exposure were identified. These were 2 cases of Stevens-Johnson syndrome and 1 case of toxic epidermal necrolysis. One of the Stevens-Johnson syndrome cases was classified assessed as probably related to parecoxib exposure by the health authority to which it was reported. The Summary of Products Characteristics was updated to include information about reported cases of these fatal skin reactions.
II/0035	Update of DDPS (Pharmacovigilance)	25/06/2009	14/07/2009	Annex II	The Detailed Description of the Pharmacovigilance System (DDPS) has been updated (version 2.0) in order to reflect various organisational changes as well as the change of the global safety database. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
II/0032	To update section 5.1, with information about the reduction of dose-dependent adverse effects following dose reduction of opioids. Section 4.2 and 4.5 were updated accordingly. In addition, section 4.2 was updated to bring the safety information (recommendations in severe renal impairment and concerning cardiovascular risk) in line with the Dynastat Core Data Sheet and the	22/01/2009	25/02/2009	SmPC and PL	For further information please refer to the Scientific Discussion (EMEA-H-381-II-32-AR).

	NSAIDS (non-selective and Cox-2 selective) labelling. The Package Leaflet has been updated accordingly. In addition, minor changes to the list of local representatives were introduced. Update of Summary of Product Characteristics and Package Leaflet				
IA/0033	IA_05_Change in the name and/or address of a manufacturer of the finished product	10/11/2008	n/a		
IA/0031	IA_09_Deletion of manufacturing site	08/11/2007	n/a		
IB/0030	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	10/09/2007	n/a		
IA/0029	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	06/06/2007	n/a		
IA/0028	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	06/06/2007	n/a	Annex II and PL	
R/0024	Renewal of the marketing authorisation.	22/02/2007	23/04/2007	SmPC, Annex II, Labelling and PL	
II/0025	Update of the Summary of Product Characteristics Update of sections 4.4 and 4.8 of the SPC, in order to reflect more accurately the increase in reports of cardiovascular events and severe skin reactions,	22/02/2007	29/03/2007	SmPC and PL	Following the assessment of the PSUR 6 covering the period from 1st April 2005 to 31st March 2006 an increased in the cardiovascular case and in the skin reactions had been observed. The CHMP requested the MAH to submit this variation to introduce the new information in the

	following the CHMP assessment of PSUR 6. The Package Leaflet has been updated to include local representatives for the two new EU Member States, Bulgaria and Romania and changes to the contact details of Estonia and The Netherlands. Update of Summary of Product Characteristics and Package Leaflet				relevant sections 4.4 and 4.8 in the SPC regarding the myocardial infarction and the skin reactions. These events were already appropriately addressed in the current approved text of the PL and no further amendments were deemed necessary. Additionally the MAH took the opportunity to include the contact details of the local representatives for Bulgaria and Romania and to update the contact details of Estonia and The Netherlands.
IA/0027	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	25/01/2007	n/a	Annex II and PL	
IA/0026	IA_09_Deletion of manufacturing site	16/01/2007	n/a		
IA/0023	IA_09_Deletion of manufacturing site	12/07/2006	n/a		
II/0022	Update of section 4.2 of the SPC and section 7 of the Package Leaflet with additional instructions to avoid problem of chemical interaction in the IV line i.e. chemical precipitation, as requested by the CHMP following the assessment of PSUR 5 covering the period from 01.04.04 to 31.03.05. The MAH took the opportunity of this variation to update the list of local representatives. Update of Summary of Product Characteristics and Package Leaflet	01/06/2006	04/07/2006	SmPC and PL	Further to the evaluation of the PSUR 5, the MAH submitted a type II variation to update the information on precipitation reactions with Dynastat when other medicinal products are given in the same intravenous line. The information was already included in section 6.2 "Incompatibilities" of the SPC. This type II variation highlights this information in section 4.2 "Posology and method of administration" of the SPC to make it more evident to users.
T/0018	Transfer of Marketing Authorisation	12/04/2006	05/05/2006	SmPC, Labelling and	Transfer of the Marketing Authorisation from Pharmacia

				PL	Europe EEIG to Pfizer Limited.
II/0021	Change(s) to the manufacturing process for the finished product . Quality changes	14/12/2005	25/01/2006	SmPC, Labelling and PL	
A18/0020	Further to a request from the European Commission to review the cardiovascular safety and the serious skin reactions of medicinal products containing celecoxib, etoricoxib, lumiracoxib, parecoxib or valdecoxib. Article 18 Review	23/06/2005	05/10/2005	SmPC and PL	Please refer to the scientific discussion: Dynastat-H-381-Art18-0020
II/0019	To update Section 4.1, 4.3 and 4.4 of the SPC following the Urgent Safety Restrictions (USR) with regard to cardiovascular safety triggered on 16 February 2005. Section 2 of the Package Leaflet (PL) has been updated accordingly. New safety warning Update of Summary of Product Characteristics and Package Leaflet	21/04/2005	10/06/2005	SmPC and PL	Further to the evaluation of the cardiovascular (CV) safety data of the class of medicnical products containing Cox-2 inhibitors (celecoxib, etoricoxib, lumiracoxib, parecoxib and valdecoxib), the CHMP concluded that an increased risk of CV adverse reactions was shown as a class effect and that there was an association between duration and dose of intake and the probability of suffering a CV reaction. Therefore, the CHMP decided, as a precautionary measure, to update the SPC through an Urgent Safety Restriction Procedure for the whole class of Cox-2 inhibitors. This Type II variation is the formal implementation of the changes in the SPC and PL for parecoxib. The adopted changes in the SPC are the following: · A contra-indication is introduced in patients with established ischaemic heart disease and/or cerebrovascular disease.

					· The warning on gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) has been strengthened. · A warning is introduced for prescribers to exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking, as well as for patients with peripheral arterial disease. · A warning is introduced for prescribers to exercise caution when prescribing NSAIDs, including valdecoxib, in combination with ACE inhibitors or angiotensin II receptor antagonists. · Information on long-term studies for valdecoxib in SAP and Alzheimer's disease has been included. To reflect these above-mentioned changes in the SPC, section 2 "Before you are given" of the Package Leaflet have been updated accordingly.
II/0017	Update of the SPC Sections 4.4 and 4.8 to strengthen the information on Severe Cutaneous Adverse Reactions, further to Post-Marketing experience. Section 4 of the PL has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	15/12/2004	26/01/2005	SmPC and PL	Section 4.4. "Special warnings and precautions for use" of the SPC is modified in order: - to state that patients receiving parecoxib are apparently at a higher risk for serious skin reactions early in the course of therapy, - to mention that erythema multiforme has been associated with the use of valdecoxib and cannot be ruled out for parecoxib, - to include additional symptoms for which the administration of parecoxib should be discontinued (e.g. mucosal lesions, other signs of hypersensitivity), - to reflect that patients without a history of sulphonamide

					allergy may also be at risk for serious skin reactions. - and to include that the frequency of serious skin reactions with valdecoxib is higher than with other COX-2 selective inhibitors. Section 4.8. "Undesirable events" of the SPC is amended to include that erythema multiforme has rarely been reported in association with the use of parecoxib.
II/0016	Update of the SPC Sections 4.3, 4.4, 4.8 and 5.1 to include safety information. The PL has been updated accordingly in section 2. Update of Summary of Product Characteristics and Package Leaflet	15/12/2004	26/01/2005	SmPC and PL	Results from two studies, in Coronary Artery Bypass Graft surgery patients (CABG II study), and a study in major general surgery patients; and from CABG I study, evaluated as part of the original MAA were presented. Increased cardiovascular thromboembolic events have been observed with high-dose valdecoxib in both cardiovascular surgery CABG studies. However, in the general surgery study, there were no differences in the overall safety profile. It has to be noted that the post-surgical use of valdecoxib in these settings is not approved in the EU.The CHMP agreed that the following sections of the SPC should be updated: - Section 4.3. "Contraindications": should mention that Dynastat should be contraindicated for the treatment of post-operative pain following CABG surgery, - Section 4.4. "Special warnings and precautions for use": has been amended to strengthen the wording on serious skin reactions, - Section 4.8. "Undesirable events": has been modified in order to clearly state that patients taking Dynastat following CABG surgery are at a higher risk of cardiovascular /thromboembolic events and deep surgical infections,

					- Section 5.1. "Pharmacodynamic properties": has been amended in order to present more clearly and in more detail the safety information from the CABG studies, and separately, the information from the General Surgery Study. The PL was updated in Section 2. "Before you are given Dynastat" in accordance with the SPC proposed changes.
II/0013	Update of the sections 4.4 and 4.8 of the SPC further to the evaluation of the PSUR covering the period from 01.04.2003 to 30.09.2003 and update of the section 6.2 of the SPC further to the evaluation of the PSUR covering the period from 01.10.2002 to 31.03.2003. Update of Summary of Product Characteristics and Package Leaflet	21/10/2004	06/12/2004	SmPC and PL	Further to the evaluation of the PSUR3 covering the period from 01.04.2003 to 30.09.2003 and PSUR2 covering the period from 01.10.2002 to 31.03.2003, the MAH submitted a type II variation to update: - sections 4.4 "Special warnings and special precautions for use", 4.8 "Undesirable effects" of the Summary of Product Characteristics (SPC), to indicate that hypersensitivity reactions (including anaphylaxis and angioedema), congestive heart failure and acute renal failure have occurred with parecoxib. - section 6.2 . "Incompatibilities" of the SPC, in order to highlight that Dynastat should not be injected into an i.v. line delivering any other drug. Following PSUR2, incompatibilities with Ondansetron (antiemetic drug), if given intravenously after parecoxib (leading to precipitation), have been reported. In addition, section 6.6 "Instructions for use and handling and disposal" of the SPC has also been modified to provide clarification on reconstitution. The PL has also been updated accordingly. In addition, the list of local representatives has been completed in the section 6 of the PL in accordance with EMEA/QRD

					templates, to include the 10 accession countries.
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/09/2004	n/a	PL	
IA/0014	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	05/07/2004	n/a		
II/0011	Update of Summary of Product Characteristics and Package Leaflet	26/02/2004	22/04/2004	SmPC and PL	
IA/0012	IA_01_Change in the name and/or address of the marketing authorisation holder	19/04/2004	n/a	SmPC, Labelling and PL	
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/01/2004	n/a	PL	
I/0008	13_Batch size of active substance	08/05/2003	n/a		
I/0006	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	08/05/2003	n/a		
II/0003	Update of Summary of Product Characteristics and Package Leaflet	18/12/2002	09/04/2003	SmPC and PL	
I/0007	24_Change in test procedure of active substance	03/04/2003	08/04/2003		
I/0005	16_Change in the batch size of finished product	03/04/2003	08/04/2003		
I/0004	15_Minor changes in manufacture of the medicinal product	03/04/2003	08/04/2003		

I/0002	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	20/11/2002	25/11/2002		
I/0001	31_Change in container shape	29/07/2002	31/07/2002		