EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Imprida HCT

Procedural steps taken and scientific information after the authorisation

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
WS/0250/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. WS-0250-G was a group of variations consisting of two Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 as follows: Variation 1: Update of section 4.5 of the SmPC to add information about the potential drug interaction between amlodipine and simvastatin, and update of the existing amlodipine information in section 4.5 in line with the revised drug interactions section for Norvasc (amlodipine monotherapy). The Package Leaflet has been updated accordingly; Variation 2: Update of section 4.5 of the SmPC to add information about the potential drug interaction between valsartan and inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter	19/07/2012	23/08/2012	SPC, PL	Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects. Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required. There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, Hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers. Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine. In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to

[1] Notifications are issued for type I variations (unless part of a group or a worksharing application). Opinions are issued for all other procedures.
[2] No Commission Decision is issued for type IA and type IB variations or for type II variations and annual re-assessments that do not affect the annexes.
[3] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0) 20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	(ritonavir). The Package Leaflet has been 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, C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia. In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin. The results of an in vitro study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.
IG/0209/G	This was an application for a group of variations. 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.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	17/08/2012	n/a		
WS/0253/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. WS-0253-G is a group of two variations (one type II & one type IB) following a worksharing procedure as follows: - Type II variation: Update of section 4.6 of the SmPC with wording on fertility in line with the SmPC for Diovan (valsartan monotherapy) and 5.3 of the SmPC to implement the changes to the SmPC for Diovan that was approved as part of a recent Article 30 (referral) procedure; - Type IB variation: Update of sections 4.6	24/05/2012	28/06/2012	SPC	The safety of amlodipine in human pregnancy has not been established. Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus. Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	and 5.3 of the SmPC to implement the changes to the SmPC for Norvasc (amlodipine monotherapy) that was approved as part of a recent Article 30 (referral) procedure. C.I.1.b - Change in the SPC, Labelling or PL following a referral procedure - The product is not covered by the defined scope of the referral but the change implements the outcome of the referral and no new additional data are submitted by the MAH, C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells. Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels. * Based on patient weight of 50 kg Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at similar doses, the changes were similar though

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
					more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.
WS/0172	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the safety and pharmacokinetic information in the SmPC related to the hydrochlorothiazide component of the fixed-dose combination. As a consequence, sections 4.2, 4.4, 4.5, 4.6, 4.8 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH has taken the opportunity to implement editorial changes in the SmPC and Package Leaflet and to update the contact details of the local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	28/06/2012	SPC, PL	The MAH has undertaken the following in-depth review of the clinical safety and clinical pharmacology information available to date on the HCTZ component of the fixed-dose combination: Review of Esidrex (containing HCTZ, first authorised in Switzerland in 1958, nationally authorised in 39 countries) PSURs 1-6 (1 Oct 1989-31 Dec 2009); Cases/events from the MAHs Global Safety Database (NGSD): NGSD was reviewed cumulatively (cut-off date 13 Apr 2010) for all cases (spontaneous reports including literature reports as well as serious adverse events from clinical trials) to identify any unlisted event clusters for Esidrex. No new unlisted event cluster was identified in the summary tabulation from the safety database search; Literature review: Major drug reference books, including Martindale (HCTZ) and Meyler's side effects (thiazide diuretics), were reviewed for unlisted adverse reactions, and bridging literature searches up to the cut-off date of 13 Apr 2010 were performed as per PSUR search criteria (publication date from the PSUR 6 cut-off date: 31 Dec 2009). As a consequence, sections 4.2, 4.4, 4.5, 4.6, 4.8 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Section 4.4 of the SmPC has been updated to include a new warning on the potential risk of 'acute angle-closure glaucoma' associated with the use of hydrochlorothiazide. Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to a week of treatment initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
					rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulphonamide or penicillin allergy. Further, the following new ADRs have been added to section 4.8 of the SmPC: asthenia, pyrexia, erythema multiforme, aplastic anemia, renal disorder, muscle spasm and acute angle-closure glaucoma.
IG/0148/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	22/02/2012	n/a		
IB/0008/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release), A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release), 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	11/11/2011	n/a		

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	and secondary packaging, for non-sterile medicinal products, B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place, B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions, B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions, B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions, B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions, B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size, B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
IG/0088/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	11/07/2011	n/a		

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	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				
IG/0073/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS, B.I.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	16/06/2011	n/a		
IG/0058	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	13/04/2011	n/a		
WS/0097	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To extend the shelf-life of the finished product from 18 months to 2 years. The MAH has also taken the opportunity to update the Annex II.B with the latest wording as per the October and November 2010 CHMP procedural announcement. 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)	17/02/2011	24/03/2011	SPC, Annex II	

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
WS/0088/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. to change the specification limit for an impurity in the active substance ; to add new test procedures for the active substance to add new specifications in the active substance to delete a test procedure for the active substance. 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.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised, B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate, B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate, B.I.b.2.e - Change in test procedure for AS	17/02/2011	17/02/2011		

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IG/0032/G	This was an application for a group of variations. Update of Summary of Product Characteristics, Labelling and Package Leaflet To implement Core Data Sheet changes in the relevant sections of the EU SmPC. The proposed changes in the SmPC are also reflected in the corresponding sections of the labelling and PL. As part of the outcome of assessment of FUM 007, 5.2 of SmPC is updated to include data from paediatric study DAP-PEDS- 07-02. The "Annex II B. Conditions for the marketing authorisation" has been updated to include the key messages of the additional risk minimisation activities described in the EU Risk Management Plan, already in place in Member States. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure 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, 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	21/12/2010	n/a	Annex II	This was an application for a group of variations. Core Data Sheet changes in the relevant sections of the EU SmPC are implemented. The proposed changes in the SmPC are also reflected in the corresponding sections of the labelling and PL. As part of the outcome of assessment of FUM 007, 5.2 of SmPC is updated to include data from paediatric study DAP-PEDS- 07-02. The "Annex II B. Conditions for the marketing authorisation" has been updated to include the key messages of the Additional Risk Minimisation Activities described in the EU Risk Management Plan, already in place in Member States. Core Data Sheet changes: Changes are made to SmPc, labelling and PL, in order to be consistent with relevant changes made to the Novartis Cubicin Basic Prescribing Information. DAP-PEDS- 07-02: A study was conducted to evaluate the pharmacokinetics of daptomycin after a single 8 mg/kg or 10 mg/kg dose of Cubicin as either a 1 or 2 hour infusion in paediatric subjects aged 2 to 6 years, inclusive, with proven or suspected Gram-positive infections who were receiving standard antibiotic therapy. The mean exposure (AUC0-8) was approximately 429 and 550 µg*hr/ml after the administration of 8 and 10 mg/kg single doses, respectively, similar to the exposure seen in adults at the 4 mg/kg dose at steady state (495 µg*hr/ml). The pharmacokinetics of daptomycin appears to be linear in the dose range studied. The half life, clearance and volume of distribution were similar at both dose levels. Risk minimisation Activities: The additional risk minimisation activities mentioned in the Risk Management Plan in the form of dosage card and laboratory susceptibility testing leaflet were in place for Cubicin because of concerns over medication errors, severe skeletal muscle toxicity and interference with coagulation tests results. It was recognised that these measures are very important for the safe and effective use of the product, hence, the CHMP recommended that this was made a condition of the Marketing Authorisation.

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	pharmacovigilance system				
IB/0007/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS, A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS, 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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	27/10/2010	n/a		
II/0005	Minor change in the manufacturing process of the active substance valsartan. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	23/09/2010	29/09/2010		
IA/0006/G	This was an application for a group of	20/09/2010	n/a		

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	variations. 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				
IB/0003/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites, 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.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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure, B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a	22/06/2010	n/a		

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	starting material/intermediate, B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate, B.III.1.a.1 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer, 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, 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				
IB/0002/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits, B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method, B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter	22/06/2010	n/a		
IA/0004	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate -	18/06/2010	n/a		

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	Up to 10-fold increase compared to the currently approved batch size				
II/0001	Changes to QPPV, Update of DDPS (Pharmacovigilance), Update of Summary of Product Characteristics	18/02/2010	26/03/2010	Annex II	