



Our Reference: BL 125495/0

Pharming Group N.V.
Attention: Mr. Matthew Moran
December 18, 2013
Sent by email:

Dear Mr. Moran:

We are reviewing your April 15, 2013 biologics license application for C1 Esterase Inhibitor (Recombinant). Based on the review of the pre-licensure safety data, your proposed pharmacovigilance plan, and the post-marketing safety reports from outside the US, we are providing the following additional recommendation:

Pharmacovigilance/Risk Management Plan

Signal detection will be performed to identify cases with identified or potential risks of rhC1INH that Data Capture Aids can then be applied to. In response to a previous information request, you provided a list of MedDRA preferred terms (PTs) that would identify specific cases with an identified or potential risk of rhC1INH. This list did not include some PTs that would help identify these adverse events (AEs) (e.g., myocardial infarction). It also included some less specific PTs that might identify additional conditions unrelated to the identified or potential risks of rhC1INH. Because of this, we compiled a list of PTs representing the most important AEs to identify in signal detection for rhC1INH (see below), as well as a more comprehensive list of PTs that can be used to identify a broader range of diagnoses or conditions categorized as one of the identified or potential risks of rhC1INH (see Appendix 1).

Please include the following MedDRA PTs among the search terms used in signal detection:

HYPERSENSITIVITY OR ALLERGIC REACTIONS	THROMBOEMBOLIC COMPLICATIONS
<ul style="list-style-type: none">○ Hypersensitivity○ Serum sickness○ Type I hypersensitivity○ Type III immune complex mediated reaction○ Anaphylactic reaction○ Anaphylactic shock○ Anaphylactoid reaction○ Anaphylactoid shock○ Angioedema○ Urticaria○ Bronchospasm○ Wheezing	<ul style="list-style-type: none">○ Embolism○ Embolism, venous○ Thrombosis○ Venous thrombosis○ Deep vein thrombosis○ Pulmonary embolism○ Pulmonary thrombosis○ Cerebrovascular accident○ Colitis, ischaemic○ Acute myocardial infarction○ Angina pectoris○ Angina, unstable○ Myocardial infarction

HYPERSENSITIVITY OR ALLERGIC REACTIONS	THROMBOEMBOLIC COMPLICATIONS
	<ul style="list-style-type: none">○ Myocardial ischaemia○ Embolic stroke○ Ischaemic stroke○ Transient ischaemic attack

Appendix 1 (below) provides a more comprehensive list of MedDRA PTs that can be used to identify a broader range of cases with the identified or potential risks of rhC1INH (including the PTs listed above in **red**), as well as complications during pregnancy or breastfeeding. This list is an example that can be used at your discretion. We are requesting that you inform FDA of the final list of terms that will be used to identify all rhC1INH identified or potential risks in signal detection (including, at minimum, the PTs in the list above).

Note: It is assumed that all listed PTs can be linked to their corresponding High Level Terms (HLTs), High Level Group Terms (HLGTs) and System Organ Class (SOC) terms, as well as corresponding Lowest Level Terms (LLTs).

Please submit your response to this information request as an amendment to this file by January 15, 2014 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

The action due date for this file is April 16, 2014.

If you have any questions, please contact me at (301) 827-6174.

Sincerely,

Nannette Cagungun, MS, PD, RAC
Regulatory Project Manager
FDA/CBER/OBRR/DBA/RPMB

Appendix 1. Relevant MedDRA or Non-MedDRA Verbatim Terms to Identified or Potential Risks of rhC1INH

HYPERSENSITIVITY REACTIONS	THROMBOEMBOLIC COMPLICATIONS	PREGNANCY OR NURSING WOMEN
<p>SOC: IMMUNE SYSTEM DISORDERS</p> <p>HLGT: Allergic conditions</p> <ul style="list-style-type: none"> HLT: Allergic conditions NEC <ul style="list-style-type: none"> PT: Allergic bronchitis PT: Allergic cough PT: Allergic respiratory symptom PT: Alveolitis, allergic PT: Asthma PT: Blepharitis, allergic PT: Bronchospasm PT: Dermatitis, allergic PT: Erythema multiforme PT: Eye allergy PT: Hypersensitivity PT: Immediate post-injection reaction PT: Infusion site hypersensitivity PT: Injection site hypersensitivity PT: Laryngitis, allergic PT: Multiple allergies PT: Pruritis, allergic PT: Reactive airways dysfunction syndrome PT: Serum sickness PT: Serum sickness-like reaction PT: Skin reaction PT: Stevens-Johnson syndrome PT: Type I hypersensitivity PT: Type III immune complex mediated reaction HLT: Allergies to foods, food additives, drugs and other chemicals <ul style="list-style-type: none"> PT: Administration related reaction PT: Allergic colitis PT: Drug eruption PT: Drug hypersensitivity PT: Drug reaction with eosinophilia and systemic symptoms PT: Infusion related reaction PT: Reaction to drug excipients PT: Toxic Epidermal Necrolysis PT: Toxic skin eruption HLT: Anaphylactic responses <ul style="list-style-type: none"> PT: Anaphylactic reaction PT: Anaphylactic shock PT: Anaphylactoid reaction PT: Anaphylactoid shock PT: First use syndrome 	<p>SOC: VASCULAR DISORDERS</p> <p>HLGT: Embolism and Thrombosis</p> <ul style="list-style-type: none"> HLT: Aortic embolism and thrombosis <ul style="list-style-type: none"> PT: Aortic embolus PT: Aortic thrombosis HLT: Cerebrovascular embolism and thrombosis <ul style="list-style-type: none"> All PTs in this category HLT: Gastrointestinal embolism and thrombosis <ul style="list-style-type: none"> All PTs in this category HLT: Hepatic and portal embolism and thrombosis <ul style="list-style-type: none"> PT: Hepatic artery embolism PT: Hepatic artery thrombosis PT: Hepatic vein thrombosis PT: Portal vein thrombosis PT: Splenic vein thrombosis HLT: Non-site specific embolism and thrombosis <ul style="list-style-type: none"> PT: Arterial thrombosis PT: Disseminated intravascular coagulation PT: Embolism PT: Embolism, arterial PT: Embolism, venous PT: Microembolism PT: Thrombophlebitis migrans PT: Thrombosis PT: Thrombotic microangiopathy PT: Venous thrombosis HLT: Peripheral embolism and thrombosis <ul style="list-style-type: none"> PT: Axillary vein thrombosis PT: Deep vein thrombosis PT: Femoral artery embolism PT: Iliac artery embolism PT: Infusion site thrombosis PT: Injection site thrombosis PT: Jugular vein thrombosis PT: Pelvic venous thrombosis PT: Penile vein thrombosis PT: Peripheral artery thrombosis PT: Peripheral embolism PT: Spinal artery embolism PT: Subclavian artery embolism PT: Subclavian artery thrombosis PT: Subclavian vein thrombosis PT: Thrombophlebitis PT: Venous thrombosis, limb HLT: Pulmonary embolism and thrombosis <ul style="list-style-type: none"> PT: Pulmonary artery thrombosis 	<p>SOC: PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS</p> <p>HLGTs:</p> <ul style="list-style-type: none"> Abortion and still birth Foetal complications Maternal complications of labour and delivery Neonatal perinatal conditions Placental, amniotic and cavity disorders (excl haemorrhages) Postpartum and puerperal disorders <p>Verbatim terms for pregnant women (non-MedDRA):</p> <ul style="list-style-type: none"> Pregnancy, labour, delivery and postpartum conditions <p>Verbatim terms for lactation (non-MedDRA):</p> <ul style="list-style-type: none"> Lactation Breastfeed Nurse Production or secretion of milk Wet nurse Suckle Colostrum

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<ul style="list-style-type: none"> HLT: Angioedemas <ul style="list-style-type: none"> PT: Angioedema PT: Circumoral oedema PT: Eyelid oedema PT: Face oedema PT: Hereditary angioedema PT: Idiopathic angioedema PT: Laryngeal oedema PT: Lip oedema PT: Lip swelling PT: Oculorespiratory syndrome PT: Oedema, mouth PT: Oropharyngeal swelling PT: Periorbital oedema PT: Pharyngeal oedema PT: Small bowel angioedema PT: Swelling face PT: Swollen tongue PT: Tongue edema HLT: Atopic disorders <ul style="list-style-type: none"> PT: Atopic keratoconjunctivitis PT: Atopy PT: Conjunctivitis, allergic PT: Dermatitis, atopic PT: Rhinitis, allergic HLT: Urticarias <ul style="list-style-type: none"> PT: Diffuse cutaneous mastocytosis PT: Haemorrhagic urticaria PT: Idiopathic urticaria PT: Infusion site urticaria PT: Injection site urticaria PT: Urticaria PT: Urticaria, papular PT: Urticaria, physical <p>SOC: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</p> <p>HLGT: Bronchial disorders (excl neoplasms)</p> <ul style="list-style-type: none"> HLT: Bronchospasm and obstruction <ul style="list-style-type: none"> PT: Asthma PT: Asthmatic crisis PT: Bronchial hyperreactivity PT: Bronchospasm PT: Reactive airways dysfunction syndrome PT: Status asthmaticus PT: Wheezing 	<ul style="list-style-type: none"> PT: Pulmonary embolism PT: Pulmonary microemboli PT: Pulmonary thrombosis PT: Pulmonary veno-occlusive disease PT: Pulmonary venous thrombosis <ul style="list-style-type: none"> HLT: Renal embolism and thrombosis <ul style="list-style-type: none"> All PTs in this category HLT: Retinal embolism and thrombosis <ul style="list-style-type: none"> All PTs in this category HLT: Site specific embolism and thrombosis NEC <ul style="list-style-type: none"> PT: Arterial thrombosis PT: Coronary artery embolism PT: Coronary artery thrombosis PT: Intracardiac thrombus PT: Ovarian vein thrombosis HLT: Vena caval embolism and thrombosis <ul style="list-style-type: none"> All PTs in this category <p>HLGT: Vascular disorders NEC</p> <ul style="list-style-type: none"> HLT: Cerebrovascular and spinal vascular disorders NEC <ul style="list-style-type: none"> PT: Cerebrovascular accident PT: Stroke in evolution HLT: Non-site specific vascular disorders NEC <ul style="list-style-type: none"> PT: Venooclusive disease <p>HLGT: Arteriosclerosis, stenosis, vascular insufficiency and necrosis</p> <ul style="list-style-type: none"> HLT: Gastrointestinal necrosis and vascular insufficiency <ul style="list-style-type: none"> PT: Colitis, ischaemic <p>SOC: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</p> <p>HLGT: Pulmonary vascular disorders</p> <ul style="list-style-type: none"> HLT: Pulmonary thrombotic and embolic conditions <ul style="list-style-type: none"> PT: Pulmonary artery thrombosis PT: Pulmonary embolism PT: Pulmonary infarction PT: Pulmonary microemboli PT: Pulmonary thrombosis PT: Pulmonary venous thrombosis HLT: Vascular pulmonary disorders NEC <ul style="list-style-type: none"> PT: Pulmonary vein occlusion PT: Pulmonary veno-occlusive disease <p>SOC: CARDIAC DISORDERS</p> <p>HLGT: Coronary artery disorders</p> <ul style="list-style-type: none"> HLT: Coronary artery disorders NEC 	

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HLGT: Upper respiratory tract disorders (excl infections) <ul style="list-style-type: none"> • HLT: Laryngeal spasm, oedema and obstruction <ul style="list-style-type: none"> ○ PT: Laryngeal oedema ○ PT: Laryngospasm ○ PT: Laryngotracheal oedema ○ PT: Stridor • HLT: Pharyngeal disorders <ul style="list-style-type: none"> ○ PT: Oropharyngeal spasm ○ PT: Oropharyngeal swelling ○ PT: Pharyngeal oedema 	<ul style="list-style-type: none"> ○ PT: Coronary artery embolism ○ PT: Coronary artery occlusion ○ PT: Coronary artery thrombosis • HLT: Ischaemic coronary artery disorders <ul style="list-style-type: none"> ○ PT: Acute coronary syndrome ○ PT: Acute myocardial infarction ○ PT: Angina pectoris ○ PT: Angina unstable ○ PT: Chest discomfort ○ PT: Chest pain ○ PT: Myocardial infarction ○ PT: Myocardial ischaemia ○ PT: Papillary muscle infarction ○ PT: Postinfarction angina ○ PT: Silent myocardial infarction <p>SOC: NERVOUS SYSTEM DISORDERS</p> <p>HLGT: Central nervous system vascular disorders</p> <ul style="list-style-type: none"> • HLT: Central nervous system haemorrhages and cerebrovascular accidents <ul style="list-style-type: none"> ○ PT: Basal ganglia infarction ○ PT: Basal ganglia stroke ○ PT: Basilar artery occlusion ○ PT: Basilar artery thrombosis ○ PT: Brain stem infarction ○ PT: Brain stem ischaemia ○ PT: Brain stem stroke ○ PT: Brain stem thrombosis ○ PT: Carotid arterial embolus ○ PT: Carotid artery occlusion ○ PT: Carotid artery thrombosis ○ PT: Cerebellar artery occlusion ○ PT: Cerebellar artery thrombosis ○ PT: Cerebellar embolism ○ PT: Cerebellar infarction ○ PT: Cerebral ischaemia ○ PT: Cerebral thrombosis ○ PT: Cerebrovascular accident ○ PT: Embolic cerebral infarction ○ PT: Embolic stroke ○ PT: Ischaemic stroke ○ PT: Lacunar infarction ○ PT: Pituitary infarction ○ PT: Precerebral artery occlusion ○ PT: Stroke in evolution ○ PT: Thalamic infarction ○ PT: Thrombotic cerebral infarction 	

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	<ul style="list-style-type: none"> ○ PT: Thrombotic stroke ○ PT: Vertebral artery occlusion ○ PT: Vertebral artery thrombosis • HLT: Cerebrovascular venous and sinus thrombosis <ul style="list-style-type: none"> ○ All PTs in this category • HLT: Transient cerebrovascular events <ul style="list-style-type: none"> ○ PT: Transient ischaemic attack 	