



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 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 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 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 |

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

| HYPERSENSITIVITY REACTIONS | THROMBOEMBOLIC COMPLICATIONS | PREGNANCY OR NURSING WOMEN |
|--|--|----------------------------|
| <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: Venocclusive 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 | |

| 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>HLGT: Upper respiratory tract disorders (excl infections)</p> <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 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 | |

| Appendix 1. Relevant MedDRA or Non-MedDRA Verbatim Terms to Identified or Potential Risks of rhC1INH | | |
|--|--|----------------------------|
| HYPERSENSITIVITY REACTIONS | THROMBOEMBOLIC COMPLICATIONS | PREGNANCY OR NURSING WOMEN |
| | <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 | |