Annex 4 - Specific adverse drug reaction follow-up forms

This annex contains the specific adverse event targeted follow-up checklists used to collect additional data for the following deferasirox RMP risks:

- Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])
- Increased liver transaminases and hepatic failure
- Gastrointestinal hemorrhage, ulcer, and esophagitis
- Hearing loss
- Lens opacities, retinal changes and optic neuritis
- Exjade severe skin reaction

Targeted follow-up checklists:

- **Exjade Serum Creatinine Increase checklist**

- In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.
-
- **Information on Dose of Exjade:**

Dose in mg/kg/day	Dates of treatment (dd/mm/yyyy)	
	Start Date	Stop Date

- **Actions taken with the suspected medication: check all that apply**
-
- **1) Was Exjade discontinued?**
- ☐ **Yes** - Date of Exjade discontinuation: ___/___/____ (dd/mm/yyyy)
- - Has serum creatinine returned to baseline after discontinuation? ☐ **Yes** ☐ **No** ☐ **Unknown**
- - Has Exjade been restarted? ☐ **Yes** ☐ **No**
- If **Yes,** restart date: ___/___/____ (dd/mm/yyyy), Dose:_____
- Re-occurrence of serum creatinine increase? ☐ **Yes** ☐ **No**☐ **Unknown**
-
- ☐ **No** - Has Exjade dose been reduced? ☐ **Yes**☐ **No**
- If **Yes,** reduction date: ___/___/____ (dd/mm/yyyy), Dose:_____
- - Has serum creatinine returned to baseline after reduction? ☐ **Yes** ☐ **No** ☐ **Unknown**
-
-
- **2) Measurement of serum creatinine**

	Date	**Serum creatinine values**	**Unit**	**Reference Range**

[@ treatment start, if available]				
[during treatment #1, if available]				
[during treatment #2, if available]				
[@ time of event]				
*[follow-up measurement @ **+30d**]*				
*[follow-up measurement @ **+60d**]*				

- **3)Renal biopsy**
- Has a renal biopsy been performed? ☐ **Yes** ☐ **No**
- If **Yes**, please provide results

- **4) Measurement of serum ferritin**

	Date	**Serum ferritin values**	**Unit**	**Reference Range**
[@ treatment start, if available]				
[during treatment #1, if available]				
[during treatment #2, if available]				
[during treatment #3, if available]				
[@ time of event]				
[follow-up measurement]				

- **Patient History:**
- Does the patient have a history of any of the following prior to the start of Exjade? **Check all that apply**
- ☐ Renal disease ☐ Congestive heart failure
- ☐ Diabetes mellitus ☐ Hypertension
- ☐ Autoimmune disease ☐ Disease of the prostate
- ☐ Other relevant history *(please specify)* ☐ None of the above
- _____
- _____
- _____
- _____
- _____

- **Concomitant medication:**
- Was the patient taking any of the following drugs? **Check all that apply**
- ☐ ACE inhibitors ☐ Diuretics ☐ Analgesics (e.g. COX-2 ☐ Immunosuppressants inhibitors, NSAIDs)
- ☐ None of the above

- List details for the above drugs as appropriate:

Drug	Route of administration	Dosing regimen or daily dose	Dates of treatment (dd/mm/yyyy)		Indication for use
			Start date	Stop date	

- **Renal Impairment or Failure checklist**

- In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

- **Event Description:**
- Did the patient present with any of the following signs or symptoms? **Check all that apply**
- ☐ Fever ☐ Increased urinary output ☐ Pain upon urinating
- ☐ Dehydration ☐ Decreased urinary output ☐ Discolored urine
- ☐ Arthralgia ☐ Difficulty starting or maintaining urine ☐ Pain around costovertebral
- ☐ Edema stream angle
- ☐ Skin rash ☐ Urinary urgency ☐ Lethargy
- ☐ Flank pain ☐ Infections ☐ Confusion
- ☐ Change in size of urine stream ☐ Burning sensation upon urinating ☐ None of the above
-
- Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s) and include dates, results and reference range for pre- and post- treatment values**
- ☐ Creatinine clearance ☐ 24-hour protein (proteinuria) ☐ Kidney biopsy
- ☐ BUN ☐ Albumin ☐ CT scan
- ☐ Serum creatinine ☐ Serum total protein ☐ Renal ultrasound
- ☐ Hemoglobin ☐ Myoglobin ☐ Cystoscopy
- ☐ CPK ☐ Electrolytes ☐ Echocardiogram
- ☐ Urinalysis ☐ Glomerular filtration rate ☐ Chest x-ray
- ☐ Metabolic Acidosis ☐ Blood pressure ☐ Abdominal x-ray
- ☐ Antinuclear antibodies ☐ C-reactive protein ☐ Magnetic resonance imaging
- ☐ Liver function tests ☐ Lipid levels ☐ Electrocardiogram
- ☐ Sedimentation rate ☐ Coagulation studies ☐ None of the above

- **Patient History:**
- Does the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply**
- ☐ Congestive heart failure ☐ Multiple myeloma ☐ Exposure to chemical dyes
- ☐ Diabetes mellitus (Type I or Type II) ☐ Urinary tract infection ☐ Myocardial infarction
- ☐ Reflux nephropathy ☐ Thromboembolic disease ☐ Coronary artery disease
- ☐ Renal disease (including nephrolithiasis) ☐ Obstructive uropathy ☐ Hypercalcemia
- ☐ Autoimmune disease ☐ Sickle cell disease ☐ History of renal transplant
- ☐ Hypertension ☐ Hyperuricemia ☐ Hepatorenal syndrome
- ☐ Extensive burns ☐ Renal arteries obstructions ☐ Hemolytic uremic syndrome
- ☐ Kidney or bladder problems/Stones ☐ Drug allergies *(please specify)* ☐ Dehydration
- ☐ Disease of the prostate ☐ Injury (crush or extensive blunt) ☐ Rhabdomyolysis
- ☐ Intravenous contrast material ☐ Hemorrhage ☐ Polycystic kidney disease
- ☐ Other relevant history *(please specify)* ☐ None of the above

- Was the patient taking any of the following drugs? **Check all that apply**
- ☐ ACE inhibitors ☐ Diuretics ☐ Analgesics (e.g. COX-2
- ☐ Immunosuppressants ☐ Antineoplastic agents inhibitors, NSAIDS)
- ☐ Lithium ☐ Vitamin D3 ☐ Antimicrobials (e.g. penicillin,
- ☐ Calcium ☐ Herbal medication (please specify) sulfonamides)
- ☐ Aminoglycosides ☐ Amphotericin ☐ Mercury
- ☐ Angiotensin II receptor blockers ☐ Diuretics ☐ Gold
- ☐ Foscarnet ☐ None of the above

Liver injury checklist

- In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

- **Event Description:**
- 1. Diagnosis and date of diagnosis
- 2. Did the patient present with any of the following signs or symptoms? **Check all that apply**
- ☐ Jaundice ☐ Ascites ☐ Asterixis (flapping tremor)
- ☐ Dark urine ☐ Fever ☐ Altered mental status
- ☐ Pale stool ☐ Fatigue ☐ Abdominal pain (specify location)
- ☐ Pruritus ☐ Bleeding (specify location) ☐ Anorexia
- ☐ Nausea ☐ Other (specify) ☐ None

- 3. Were any of the following diagnostic tests performed?
- ►**If yes, please specify the dates and results including reference range and pre- and post- treatment values.**
- ☐ Liver function tests

- ☐ Serology & PCR testings for Hepatitis A, B, C &/or E virus
- ☐ Autoantibody test
- ☐ Abdominal or hepatobiliary ultrasound
- ☐ Abdominal CT scan
- ☐ Liver biopsy
- ☐ Liver transplant (planned or completed)
- ☐ Other (specify)
- ☐ None
-
- **Does the patient have a history of any of the following prior to the start of the suspect drug? Check all that apply and include date(s) of onset as well as status (i.e. active/inactive) and details**
- ☐ Previously elevated liver enzymes☐ Tattoos
- ☐ Hepatitis☐ Transfusion or blood product administration
- ☐ Other hepatobiliary disease or dysfunction☐ Gilbert's disease
- ☐ Autoimmune disease☐ Alcohol intake
- ☐ Active pancreatitis☐ Drug abuse
- ☐ Diabetes mellitus (Type I or II)☐ Foreign travel
- ☐ Non alcoholic steatohepatitis☐ Active gall bladder disease
- ☐ None ☐ Other (specify)
- **Has the patient recently (i.e. within the past 6 months) taken any of the following? Check all that apply**
- ☐ Sulfonamides ☐ Furosemide☐ ACE Inhibitors
- ☐ Valproic acid ☐ NSAIDS (e.g. ibuprofen) ☐ Estrogens (oral contraceptives)☐ Metronidazole ☐ Acetaminophen/Paracetamol☐ Amiodarone
- ☐ COX II inhibitors(e.g. celecoxib)☐ Tetracycline☐ Steroids
- ☐ Thiazide diuretics☐ 6-Mercaptopurine☐ Statins
- ☐ Nicotinic acid☐ Methotrexate☐ Other (specify)
- ☐ None
-

• Exjade Gastrointestinal Ulcers & Bleed checklist

- In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.
-
- **Event Description:**

- Did the patient experience any of the following signs or symptoms before the GI bleed/ulcer developed? **Check all that apply & specify time to onset from first starting Exjade, time of occurrence during the day in relation to Exjade ingestion, severity, and frequency, if applicable**
-

Symptom	Time to onset from first starting Exjade	Time of occurrence during the day in relation to Exjade ingestion	Severity (mild, moderate, severe)	Frequency (e.g. daily, once weekly, three times monthly)
☐ Nausea				
☐ Abdominal pain				

☐ Epigastric tenderness/pain				
☐ Vomiting				
☐ Dyspepsia				
☐ Other (specify):				

- Provide the platelet count at baseline (start of Exjade) and at the time of the bleed? At baseline _____
- At time of bleed _____
- Were any of the following diagnostic tests/procedures performed? **Check all that apply and specify dates and results**
- ☐ *H. Pylori* ___/___/____ (dd/mm/yyyy) Results: _____
- ☐ Endoscopy ___/___/____ (dd/mm/yyyy) Results: _____
- ☐ Tissue/mucosal biopsy ___/___/____ (dd/mm/yyyy) Results: _____
- ☐ Other – please specify:
- _____ ___/___/____ (dd/mm/yyyy) Results: _____
- ☐ None of the above
- **Patient History:**
- Does the patient have a history of any of the following? **Check all that apply**
- ☐ Epigastric pain ☐ Esophagitis
- ☐ Gastritis ☐ Gastrointestinal bleed
- ☐ Gastrointestinal ulcer ☐ Hemorrhoids
- ☐ Bleeding disorders/abnormal coagulation tests ☐ Other relevant history – please specify:
- ☐ None of the above _____
- Was the patient taking any of the following drugs at the time of event? **Check all that apply**
- ☐ Anticoagulants ☐ Bisphosphonates
- ☐ NSAIDs ☐ Steroids
- ☐ None of the above
- Has the patient ever used any of the following drugs? **Check all that apply**
- ☐ Antacids ☐ Proton pump Inhibitors
- ☐ H2 blockers ☐ None of the above
- **Exjade Hearing Loss checklist**

- In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

- **Event Description:**
- Which of the following describes the hearing loss? **Check all that apply**
- ☐ **Unilateral hearing loss** or ☐ **Bilateral hearing loss**
- ☐ **Sensorineural hearing loss** or ☐ **Conductive hearing loss**
- Further description of the event (if necessary):_____
- _____
- _____
- _____
- Were any relevant investigations performed (e.g. audiometry testing or reports from specialists if consulted)?
- ☐ **Yes**, Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____
- Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____
- Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____
- Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____
- ☐ **No** ☐ **Unknown**
- **Patient History:**
- Does the patient have a history of **Ear problems** prior to the start of the suspect drug? ☐ **Yes** ☐ **No**
- **If yes, please specify**: ☐ **Other ear disorders** (Please specify):
- _____ _____
- _____ _____
- _____ _____
- _____ _____
- **Follow-up:**
- **1) Was Exjade discontinued?**
- ☐ **Yes** - Was there any improvement in the hearing loss after discontinuation? ☐ **Yes** ☐ **No**
- - Has Exjade been restarted? ☐ **Yes** ☐ **No**
- If **Yes,** restart date: ___/___/____ (dd/mm/yyyy), Dose:_____
- Re-occurrence of hearing loss? ☐ **Yes** ☐ **No**
- ☐ **No** - Has Exjade dose been reduced? ☐ **Yes** ☐ **No**
- If **Yes,** reduction date: ___/___/____ (dd/mm/yyyy), Dose:_____
- - Was there any improvement in the hearing loss after reduction? ☐ **Yes** ☐ **No**
- **2) Measurement of serum ferritin**

	Date	Serum ferritin values	Unit	Reference Range
[@ treatment start, if available]				
[during treatment #1, if available]				
[during treatment #2, if available]				
[during treatment #3, if available]				
[@ time of event]				
[follow-up measurement]				

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- **Exjade Lens Opacities/Cataracts checklist**

- In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.
-
- **Event Description:**
- Which of the following describes the lens opacity? **Check all that apply**
-
- ☐ **Unilateral**
- or
- ☐ **Bilateral**
-
- ☐ **Punctuate lens opacities**
- or
- ☐ **Complete cataract formation**
-
- Further description of the lens opacity (e.g. size):
_____
_____
_____
_____
__
-
- Were any relevant investigations performed (e.g. ophthalmology testing or reports from specialists if consulted)?
- ☐ **Yes**, Test:_____ Date:___/___/____ (dd/mm/yyyy)
Results:_____
- Test:_____ Date:___/___/____ (dd/mm/yyyy)
Results:_____
- Test:_____ Date:___/___/____ (dd/mm/yyyy)
Results:_____
- Test:_____ Date:___/___/____ (dd/mm/yyyy)
Results:_____
- ☐ **No** ☐ **Unknown**
-
- **Patient History:**
- Does the patient have a history of **Lens opacities / Cataracts** prior to the start of the suspect drug? ☐ **Yes** ☐ **No**
- **If yes, please specify**: ☐ **Other eye disorders** (Please specify):
- _____ _____
- _____ _____
- _____ _____

- _____ _____
-
- **Follow-up:**
- **1) Was Exjade discontinued?**
- ☐ **Yes** - Was there any improvement in the lens opacity after discontinuation? ☐ **Yes** ☐ **No**
- - Has Exjade been restarted? ☐ **Yes** ☐ **No**
- If **Yes,** restart date: ___/___/____ (dd/mm/yyyy), Dose:_____
- Re-occurrence of lens opacity? ☐ **Yes** ☐ **No**
-
- ☐ **No** - Has Exjade dose been reduced? ☐ **Yes** ☐ **No**
- If **Yes,** reduction date: ___/___/____ (dd/mm/yyyy), Dose:_____
- - Was there any improvement in the lens opacity after reduction? ☐ **Yes** ☐ **No**
-
- **2) Measurement of serum ferritin**

	Date	**Serum ferritin values**	**Unit**	**Reference Range**
[@ treatment start, if available]				
[during treatment #1, if available]				
[during treatment #2, if available]				
[during treatment #3, if available]				
[@ time of event]				
[follow-up measurement]				

-
- **Exjade Severe Skin Reaction Checklist**

- In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that apply**

☐ Infiltration ☐ Itching ☐ Headache
☐ Blistering of rash ☐ Joint aches ☐ Body aches
☐ Desquamation (skin loss)/skin peeling ☐ Visual symptoms ☐ Electrolyte imbalances
(please specify %) ☐ General ill feeling ☐ Eating/Swallowing difficulties
☐ Nikolsky's symptom ☐ Fever ☐ Genital lesions
☐ Involvement of mucous membrane ☐ Chills ☐ Necrosis
☐ Rash ☐ Cough
Was the rash associated with any other systemic symptoms or abnormalities? ☐ None of the above
☐ Yes (*please describe)* ☐ No ☐ Unknown ☐ Other *(please specify)*

Time to onset of general symptoms after starting suspected medication?

Time to onset of cutaneous symptoms after starting suspected medication?

Description of lesion(s) on the skin: (type [erythematic, papules, plaques, eczema, blisters, etc. with estimated % of body surface], topography [sun exposed areas only, trunk and upper extremities, face, etc.], start and stop date(s) of skin lesion[s])

Was there a final diagnosis?
☐ **Yes** *(please describe and whether it was confirmed by a dermatologist* ☐ **No** ☐ **Unknown**

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s), dates and results**

- ☐ Skin lesion biopsy
- ☐ Immunofluorescence testing
- ☐ Microscopic examination of skin
- ☐ Genetic test
  - ►Was genotyping of HLA (Human Leukocyte Antigen) done? ☐ Yes ☐ No ☐ Unknown
  - ►Was HLA-B*1502 allele positive? ☐ Yes ☐ No ☐ Unknown
  - ►Was HLA-A*3101 allele positive? ☐ Yes ☐ No ☐ Unknown
- ☐ None of the above

Relevant medical history (concurrent and pre-existing conditions)
(Please specify medical condition and date of onset)

Does the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply**

- ☐ Herpes simplex
- ☐ Streptococcal infection
- ☐ Immunization *(please specify)*
- ☐ Drug allergy *(please specify)*
- ☐ HIV
- ☐ Influenza
- ☐ Typhoid
- ☐ Excessive UV light exposure
- ☐ Carrying HLA-B12 gene
- ☐ Graft-versus-host disease
- ☐ Staphylococcal infection
- ☐ Mycoplasma pneumonia
- ☐ Bone marrow or organ transplant
- ☐ Non-drug allergy *(please specify)*
- ☐ Hepatitis
- ☐ Diphtheria
- ☐ Radiation therapy
- ☐ Systemic lupus erythematosus
- ☐ None of the above
- ☐ Other relevant history *(please specify)*

Was the patient taking any of the following drugs? **Check all that apply**

- ☐ Anticonvulsants (e.g. phenytoin)
- ☐ Sulfonamide antibiotics
- ☐ Non-sulfonamide antibiotics
- ☐ Barbiturates
- ☐ NSAIDS
- ☐ Allopurinol
- ☐ Acetaminophen/Paracetamol
- ☐ Corticosteroids
- ☐ None of the above

Please indicate the treatment (if any) provided to the patient for this event.
Please specify treatment (corticosteroids, cyclophosphamide, other)

Drug	Dose	Dates (Start-Stop)

Outcome of event (include date if appropriate):

Action taken with Deferasirox with regard to event (include date if appropriate):