Supplementary information

Home-based infusion of alglucosidase alfa can safely be implemented in adults with late-onset Pompe disease; lessons learned from 18380 infusions.

BioDrugs

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Online resource 1: Classification of AEs and IARs [1]

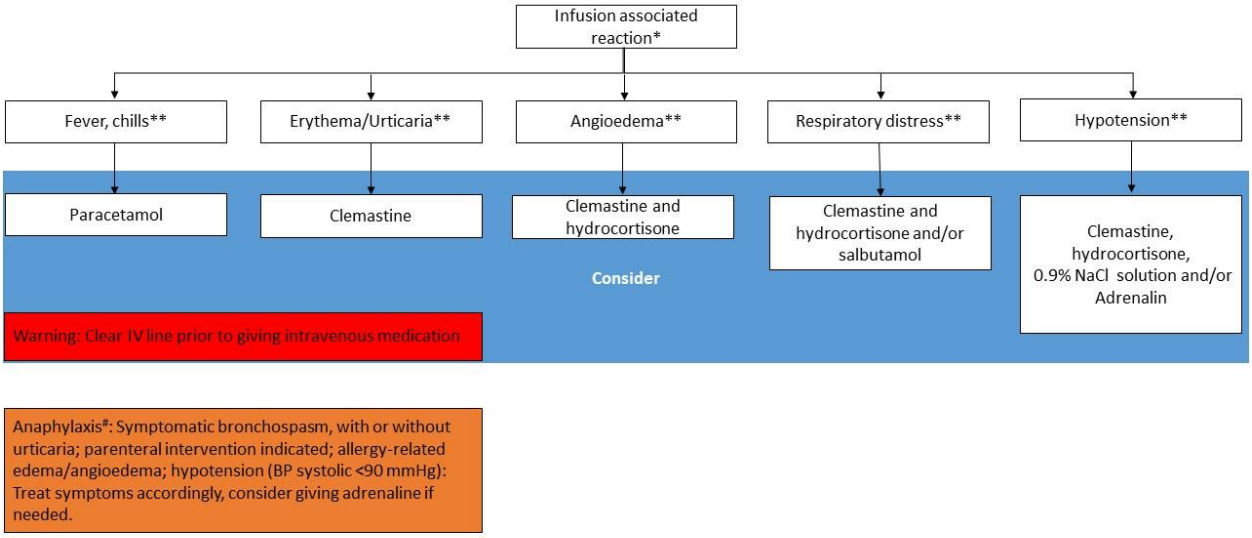
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing, undressing, feeding self, using the toilet, taking medications, and not bedridden.

[1] van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med. 2010;362(15):1396-406.

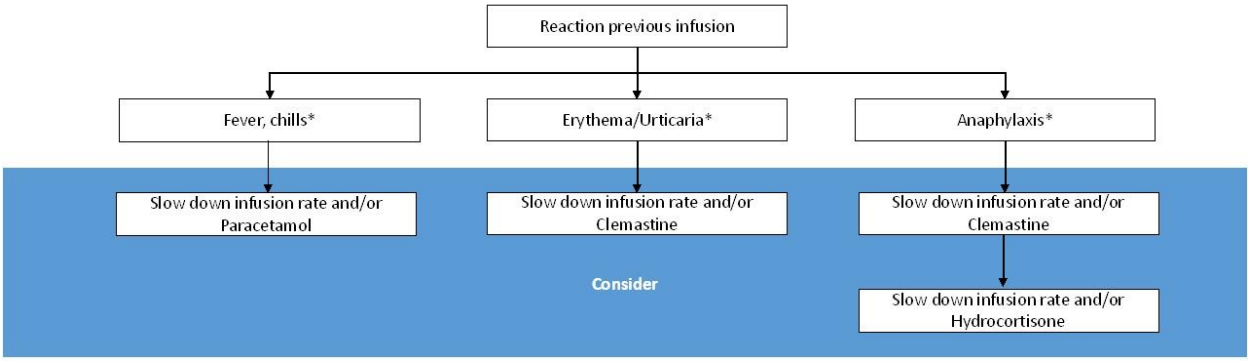
Online resource 2: Medication to be administered during an IAR (A) and actions and premedication to be considered for the subsequent infusion(s) (B) to prevent IARs

A. Medication during an IAR → acute reaction



*Different symptoms may occur at the same time
** Most common symptoms listed, multiple symptoms may occur at the same time. For additional symptoms and their classification see CTCAE classification, in case of worsening clinic, reassess.
#See CTCAE classification

B. Premedication



* Most common symptoms listed, multiple symptoms may occur at the same time. For additional symptoms and their classification see CTCAE classification.

Medication during an IAR and actions and premedication to be considered prior to the subsequent infusions A: Medication during an IAR in the acute situation. B: Premedication and other interventions to be considered the next infusion after an IAR has occurred. NaCl= Sodium Chloride, IV=intravenous, BP= Blood pressure, CTCAE= Common Terminology Criteria for Adverse Events.

Online resource 3: Types of IARs

	Hospital	Home
Type of IAR, n (% of the total number of symptoms registered*)		
- **Total**	307 (100%)	187 (100%)
- **Itching**	37 (12.1%)	11 (5.9%)
- **Chills**	31 (10.1%)	43 (23.0%)
- **Headache**	28 (9.1%)	0 (0.0%)
- **Localised exanthema**	28 (9.1%)	8 (4.3%)
- **Chest discomfort**	16 (5.2%)	15 (8.0%)
- **Hypertension**	14 (4.6%)	2 (1.1%)
- **Urticaria**	14 (4.6%)	24 (12.8%)
- **Sub febrile temperature**	13 (4.2%)	1 (0.5%)
- **Generalised exanthema**	12 (3.9%)	2 (1.1%)
- **Tachycardia**	12 (3.9%)	0 (0.0%)
- **Flushing**	11 (3.6%)	2 (1.1%)
- **Dyspnoea**	9 (2.9%)	1 (0.5%)
- **Nausea**	8 (2.6%)	2 (1.1%)
- **Hyperthermia or fever**	7 (2.3%)	1 (0.5%)
- **Malaise**	6 (2.0%)	1 (0.5%)
- **Coughing**	5 (1.6%)	2 (1.1%)
- **Fatigue**	5 (1.6%)	0 (0.0%)
- **Dizziness**	4 (1.3%)	3 (1.6%)
- **Desaturation**	4 (1.3%)	1 (0.5%)
- **Localised angioedema**	3 (1.0%)	10 (5.3%)
- **Palpitations**	3 (1.0%)	0 (0.0%)
- **Excess sweating**	2 (0.7%)	0 (0.0%)
- **Musculoskeletal pain**	2 (0.7%)	4 (2.2%)
- **Pallor**	2 (0.7%)	6 (3.2%)
- **Agitation**	1 (0.3%)	0 (0.0%)
- **Oedema**	1 (0.3%)	0 (0.0%)
- **Paraesthesia**	1 (0.3%)	0 (0.0%)

- **Trembling**	1 (0.3%)	38 (20.3%)
- **Vomiting**	1 (0.3%)	2 (1.1%)
- **Bradycardia**	1 (0.3%)	0 (0.0%)
- **Other**[#]	25 (8.1%)	8 (4.3%)

*Patients may have had more than one symptom per IAR; percentages are the percentage of the total number of symptoms in the hospital or at home, respectively. [#]Other being: Itchy throat, localised erythema, tingling/squeezing sensation throat, tingling sensation mouth, strange feeling in the oesophagus, stomach ache, feeling warm/hot, drowsy, increased mucus production, tingling sensation cheek, sensitive palate, hypotension, and dry mouth, hyperglycaemia, heartburn, gagging, cyanosis, cold hands, and nose, brain fog, atrial fibrillation, weird feeling, swollen throat, feeling warm and atrial fibrillation, hypotension and light-headedness and uncomfortable feeling gastric region and dirty flavour in the mouth. IAR= Infusion-associated reaction.

Online resource 4: Medication and interventions prior to and in response to IARs

	Hospital	Home
Most severe intervention needed, n (% of the total number of IARs)		
- **Total**	144 (100%)	113 (100%)
- **None taken**	33 (22.9%)	82 (72.6%)
- **Other medication was given***	26 (18.1%)	1 (0.9%)
- **Antihistamine was given**	26 (18.1%)	9 (8.0%)
- **Paused infusion, restarted infusion later**	26 (18.1%)	14 (12.4%)
- **Stopped infusion completely****	16 (11.1%)	6 (5.3%)
- **Corticosteroid was given**	8 (5.6%)	0 (0.0%)
- **Antihistamine and corticosteroid were given**	4 (2.8%)	0 (0.0%)
- **Set infusion back to the previous step**	2 (1.4%)	0 (0.0%)
- **The patient required immediate clinical evaluation in the hospital**	1 (0.7%)	1 (0.9%)
- **Not reported**	2 (1.4%)	0 (0.0%)
Premedication prior to infusion with IAR, n (% of the total number of IARs)		
- **Total**	144 (100%)	113 (100%)
- **No premedication**	48 (33.3%)	91 (80.5%)
- **Antihistamine and Corticosteroid**	32 (22.2%)	0 (0.0%)
- **Antihistamine**	30 (20.8%)	7 (6.2%)
- **Antipyretic, Corticosteroid and other*****	15 (10.4%)	0 (0.0%)
- **Corticosteroid**	10 (6.9%)	0 (0.0%)
- **Corticosteroid and other*****	4 (2.8%)	0 (0.0%)
- **Antipyretic and Corticosteroid**	3 (2.1%)	0 (0.0%)
- **Antihistamine and Antipyretic**	1 (0.7%)	0 (0.0%)
- **Antipyretic**	0 (0.0%)	14 (12.4%)
- **Not reported**	1 (0.7%)	1 (0.9%)
Action taken next infusion (most severe), n (% of the total number of IARs)		
- **Total**	144	113

- **The patient received premedication**	82 (56.9%)	21 (18.6%)
- **The infusion schedule was adapted**	26 (18.1%)	8 (7.1%)
- **None taken**	23 (16.0%)	79 (69.9%)
- **The next infusion was given in a hospital setting**	2 (1.4%)	4 (3.5%)
- **Other[#]**	9 (6.3%)	1 (0.9%)
- **Not reported**	2 (1.4%)	0 (0.0%)
Premedication next infusion, n (% of the total number of IARs)		
- **Total**	144 (100%)	113 (100%)
- **No premedication**	39 (27.1%)	89 (78.8%)
- **Antihistamine and Corticosteroid**	39 (27.1%)	0 (0.0%)
- **Antihistamine**	30 (20.8%)	11 (9.7%)
- **Antipyretic, Corticosteroid and other [##]**	14 (9.7%)	0 (0.0%)
- **Corticosteroid**	10 (6.9%)	0 (0.0%)
- **Corticosteroid and other [##]**	5 (3.5%)	0 (0.0%)
- **Antipyretic and Corticosteroid**	4 (2.8%)	0 (0.0%)
- **Antihistamine and Antipyretic**	2 (1.4%)	0 (0.0%)
- **Antipyretic**	0 (0.0%)	13 (11.5%)
- **Not reported**	1 (0.7%)	0 (0.0%)

* Other being: Paracetamol, corticosteroid and paracetamol and codeine and insulin, corticosteroid and beta blocker, paracetamol and nose spray, paracetamol and antihypertensive, corticosteroid and paracetamol and codeine, paracetamol and codeine. **infusion during which the IAR occurred was not restarted again (on the same day) after the IAR occurred. *** Other being: Beta-blocker, codeine. [#] Other being: Discontinued therapy, cardiologist visit before next infusion, allergy testing and possible desensitisation protocol, antihypertensives and or beta blocker is given at next infusion, the patient was switched from alglucosidase alfa produced in 4000L tanks to alglucosidase alfa that was produced in 2000L tanks, no infusion plaster. [##] Other being: Beta-blocker, codeine. IAR= Infusion-associated reaction.

Online resource 5: Severe IARs

The five severe infusion-associated reactions reported in this study occurred in 3 different patients, two of whom had two severe IARs. The first patient experienced the first severe IAR in the home and the second in the hospital. Years prior to the severe IARs (an SAE), the patient had experienced 30 mild IARs with urticaria at home. These had been controlled for years by pausing the infusion, using antihistamines, and adapting the infusion schedule. The patient had been treated with ERT for nine years and received home therapy for 8 years and 2 months. She experienced stabbing chest pain with coughing reflex, redness in the face with itching, and red blisters on the throat after 45 minutes during a home infusion. Symptoms were relieved with clemastine, ondansetron, and fentanyl, and the infusion was discontinued. However, the chest pain returned the next day, and a Non-ST-elevation myocardial infarction was diagnosed. The patient, aged 45, had no cardiac history prior to this and only had hypothyroidism in her medical history. The patient received her next infusion in the hospital but again developed coughing, redness of the face, and a strange sensation in the chest after one hour of infusion. This was followed by the development of generalised exanthema, urticaria on arms, trunk, and neck, increased mucus production in the throat, fluid retention, chills, and a tight sensation in the throat. The infusion was paused, and clemastine, hydrocortisone, and salbutamol were given, which relieved the symptoms. The infusion was discontinued. Despite premedication with clemastine and adjusting the infusion schedule with slower incremental steps, the patient still developed a moderate and mild IAR during subsequent infusions. At the patient's request, ERT was discontinued due to the IARs, with the possibility of recommencing it in the event of further deterioration. To date, ERT with alglucosidase alfa has not been restarted in this patient.

A second patient experienced two severe IARs in the hospital. This patient had been treated with ERT for one year and three months and had a medical history of a duodenal ulcer, hypersensitivity to contrast agents, and an inhalation allergy to dust mites. She had previously experienced two IARs. One mild IAR over a year ago and a moderate IAR during the infusion prior to this one, for which her infusion schedule was adapted (steps prolonged to 45 min) and premedication (clemastine) was started. During the last step, the infusion ran subcutaneously, after which the patient developed generalised exanthema and itching. The infusion was stopped, and another dose of clemastine was given orally. Symptoms did not subside, and hydrocortisone was administered as the patient developed nausea, progressive exanthema, and a sub-febrile temperature, which relieved the symptoms. The infusion was then discontinued. Her infusion schedule was adapted further, and clemastine and hydrocortisone were given

as premedication at the next infusion, but she again developed generalised exanthema, itching, and nausea. The infusion was stopped and not restarted, and another dose of clemastine (1 mg) was given, which relieved the symptoms. After this infusion, the treatment with alglucosidase alfa was permanently discontinued as per the patient's request. To date, ERT with alglucosidase alfa has not been restarted in this patient.

The third patient already received 2 mg clemastine as premedication because of previous allergic reactions to other medications. He had a medical history of deep venous thrombosis, ulcerative colitis, autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome, erysipelas, and lichen planus. This patient had been treated with ERT for less than two months and had received 4 infusions with alglucosidase alfa prior. Two and a half hours into the infusion, the patient developed itching, generalised exanthema with urticaria on both arms, and increased blood pressure and temperature, for which the infusion was stopped. An additional dosage of 2 mg clemastine, as well as 100 mg hydrocortisone, was administered. Symptoms subsided, but the infusion was not restarted. For the next infusion, hydrocortisone (100 mg) was added to the premedication, and the last infusion step was reduced from 250 ml/h to 125 ml/h. Unfortunately, the patient experienced two more mild and four more moderate IARs, and the treating physicians decided to completely stop treatment with alglucosidase alfa. The patient passed away about 4 years later due to acute liver failure caused by autoimmune hepatitis.

Online resource 6: Standard infusion schedules used in the Erasmus MC and an example of a slow infusion scheme

		0.2 mg/kg/h	**0.8 mg/kg/h**	**3.5 mg/kg/h**	**10 mg/kg/h**
Weight Range (kg)	**Total volume (ml)**	**Step 1 (ml/h) for 30 minutes**	**Step 2 (ml/h) for 30 minutes**	**Step 3 (ml/h) for 30 minutes**	**Step 4 (ml/h) Remainder of infusion volume**
20.1-30	150	1.5	6	26	75
30.1-40	200	2	8	35	100
40.1-50	250	2.5	10	44	125
50.1-60	300	3	12	53	150
60.1-100	500	5	20	88	250
100.1-120	600	6	24	105	300
120.1-140	700	7	28	123	350
140.1-160	800	8	32	140	400
160.1-180	900	9	36	158	450
180.1-200	1000	10	40	175	500

Table 1: Standard infusion rate schedule for late onset patients treated with 20 mg/kg.

Slow infusion rate	
Mg/kg/h	**Duration in minutes**
0.018	15
0.04	15
0.06	15
0.08	30
0.16	60
0.5	60
3.8	15
37	60
15	rest

Table 2: Slow infusion schedule.