Product ADR Table

ADR (Number of ADRs)	Date detected	Source	Label against USPI (Yes / No)	Valid (Yes/No)	Period 1 (07 Jan 2020 to 06 Apr 2020)	Period 2 (07 Jan 2019 to 06 Jan 2020)	Period 3 (07 Jul 2017 to 31 Dec 2019)	Period 4 (07 Jul 2017 to 06 Apr 2020)	Comments
Diarrhoea	31-Jul-18	Database	No	No	7	7	37	44	Overall 44 cases of diarrhoea have been reported till date. The event was serious in 03 cases requiring hospitalization and non-serious in remaining 41 cases. Out of the 44 reported cases of diarrhoea, in 02 cases, the event resolved after endari was withdrawn (positive dechallenge). In 01 case, the dosage was maintained and the event resolved while in 01 case information on outcome was not available. In 02 cases, the event recovered after dose of Endari was reduced, while in 01 case, endari was discontinued and the event was not resolved.In 01 case, the event was attributed to viral infection. In 01 case, the patient wasn't taking medication with food as indicated while in 01 case the event occurred as the patient was taking sugar with the juices. In 01 case, the event was a result of interaction between endari and voxelotor. In rest of the 33 cases the event could be either confounded by multiple concomitant medications or limited case details were availabe. Also, diarrhoea can be explained by the underlying condition sickle cell disease. In view of these facts, this event is not considered as a signal at this moment, but a continuous monitoring will be performed to further evaluate this event as a signal.
Fatigue	31-Jul-18	Database	No	No	1	6	16	18	Overall 18 cases of fatigue were reported with Endari till date. The event was assessed as serious in 01 case requiring hospitalization and non-serious in remaining 17 cases. In 01 case, the patient was hospitalized due to extreme exhaustion after taking Endari and hence Endari was discontinued; the outcome was unknown. In another 01 case, the event resolved after Endari was discontinued. In 02 cases, the event could be explained by concomitant medications like levetiracetam and in 01 case the event can be explained by underlying sickle cell disease. In 02 cases, the event was attributed to concurrent stomach pain and low platelet count. In the remaining 11 cases, there was limited clinical information for proper case assessment. Considering the fact that fatigue is an expected occurrence in patients with underlying sickle cell disease, this event is not considered as a safety concern as of now.
Infection	31-Jul-18	Database	No	No	1	0	9	10	Overall 10 cases of infection were reported with Endari till date. The event was assessed as non-serious in 02 cases and serious in the remaining 08 cases requiring hospitalization. In 01 case, it was reported that infection was due to underlying sickle cell disease and in the remaining 09 cases the underlying cause of infection was unknown. In view of limited clinical details for assessment of the cases, and infection being common in patients with underlying sickle cell disease, this event is not considered as a safety concern as of now.
Malaise	31-Jul-18	Database	No	No	3	12	23	27	Overall 27 cases of malaise were reported with Endari till date. The event was assessed as non-serious in 22 cases and serious (Hospitalization) in 05 cases. In 03 cases, there was positive dechallenge; in 02 cases, the event could be attributed to sickle cell disease crisis and associated event of back pain aggravation; in 01 case, the event occurred on the same day of start the therapy. In the remaining 21 cases, due to limited clinical information and considering the fact that malaise is an expected occurrence in patients with underlying sickle cell disease, this event is not considered as a safety concern as of now.
Migraine	31-Jul-18	Database	No	No	1	0	5	6	Overall 06 cases of migraine were reported till date. The event was serious in 01 case and non-serious in remaining 05 cases. Only in 01 of the reported 06 cases, there was compatible temporal association between the onset of migraine and therapy with Endari, whereas in the remaining 05 cases there was limited clinical information. Hence, this event is not considered as a safety concern as of now.
Pruritus	31-Jul-18	Database	No	No	3	4	13	16	Overall 16 cases of pruritus were reported with Endari till date and the event was assessed as non-serious in all the cases. Of these 16 cases, in 01 case dechallenge was poistive, in 02 cases the event resolved while drug was till ongoing, in 01 case, the event was not resolved on discontinuation of drug, 01 case, action taken with drug and event outcome was unknown. In 03 cases, the event could be confounded by concomitant medications like zolpidem, amlodipine and hydromorphone while in the remaining 08 cases there was limited clinical information. The event can alternately explained by underlying sickle cell disease. Hence, this event is not considered as a safety concern as of now.
Vomiting	31-Jul-18	Database	No	No	3	5	21	24	Overall 24 cases of vomiting were reported with Endari till date and the event was assessed as non-serious in all the cases. In 02 cases, de-challenge was positive and in 05 cases there was a temporal relationship; however, information was limited about the patient's medical history, concomitant medication, action taken with suspect drug and event outcome, for proper case assessment. In 01 case, the event can be explained by associated event of motion sickness; in 01 case the event can be explained by underlying pain crisis. In the remaining 15 cases, information was limited for a proper case assessment. This event is not considered as a safety concern as of now.
Weight increased	31-Jul-18	Database	No	No	2	4	13	15	Overall 15 cases of weight increased reported with Endari till date and the event was assessed as non-serious in all the cases. In 02 cases, there was temporal association, however action taken with drug was unknown and event was not resolved while in 01 case, the event was attributed to overeating. In rest of the 12 cases, there was limited clinical information precluding further assessment. Hence this event is not considered as a safety concern as of now.

Abdominal discomfort	29-Oct-18	Database	No	No	7	6	21	28	Overall 28 cases of abdominal discomfort have been identified till date. The event was serious (hospitalization) in 01 case and non-serious in rest of 27 cases. Out of 28 cases, in 01 case, the event resolved after Endari was discontinued; in 04 cases there was no information on outcome of the event and in 01 case, event recovered while endari was continued. In 4 cases, the event could be attributed to the associated events like motion sickness, diarrhea, abdominal pain and vomiting; in 01 case, the event could be explained by surgical history of gastric bypass and in 01 case, the event was due to viral infection. In the remaining 16 cases, there was eithre limited clinical details or there were other confounding factors like multiple concomitant medications. As per the PI, patients can experience abdominal pain and the event abdominal discomfort is a non-specific term. In view of these facts, this event is not considered as a safety concern as of now.
Abdominal pain (inc. upper abdominal pain)	29-Oct-18	Database	Yes	No	4	34	80	84	This is a listed event.
Back pain	29-Oct-18	Database	Yes	No	10	3	22	32	This is a listed event.
Constipation	29-Oct-18	Database	Yes	No	5	15	38	43	This is a listed event.
Dyspepsia	29-Oct-18	Database	Yes	No	0	1	4	4	This is a listed event.
Dyspnoea	29-Oct-18	Database	No	No	0	0	2	2	Overall 02 cases of dyspnoea were reported with Endari till date and the event was assessed as non-serious in all the cases. In all the cases, there was limited clinical information to analyse the underlying cause for dyspnoea. Hence, this event is not considered as a signal at this moment, but a continuous monitoring will be performed to further evaluate this event. Note: The event met the frequency of 03 on 29 Oct 2018. However as per current frequency, the case count is 02.
Headache	29-Oct-18	Database	Yes	No	8	19	37	46	This is a listed event.
Hip arthroplasty	29-Oct-18	Database	No	No	0	1	4	4	Overall 04 cases of hip arthroplasty were reported with Endari till date and the event was assessed as serious in all the cases. In 01 case, the patient had avascular necrosis as a complication to underlying sickle cell disease and underwent hip arthroplasty. In 3 cases, there was limited clinical information regarding the underlying cause for hip arthroplasty. Moreover considering the nature of the event, this is not considered as a safety concern as of now.
Nausea	29-Oct-18	Database	Yes	No	3	29	82	86	This is a listed event.
Pain NOS	29-Oct-18	Database	No	No	15	13	52	68	Considered covered under similar events mentioned in PI like Chest pain, back pain, limb pain, abdominal pain are labelled.
Pyrexia	29-Oct-18	Database	No	No	2	4	13	16	Overall 16 cases of pyrexia were reported till date. The event was assessed as serious (hospitalization) in 09 cases and non-serious in 07 cases. Of these 16 cases, in 02 cases, a event canbe confounded by the associated condition of pneumonia and in rest of the 14 cases, there was limited clinical information. Considering the nature of the event and the fact that patients with sickle cell disease are prone to have infections resukting in fever, this event is not considered as a safety concern as of now.
Surgery	29-Oct-18	Database	No	No	0	2	11	11	Overall 11 cases of surgery were reported with Endari till date and the event was aassessed as serious in all the cases. The underlying cause for surgery was not known for all the cases. Moreover considering the nature of the event, this is not considered as a safety concern as of now.
Weight decreased	29-Oct-18	Database	No	No	2	3	7	10	Overall 10 cases of decreased weight were reported with Endari till date and the event was assessed as non-serious in all the case. In 01 case, the event was due to decreased oral intake and in the remaining 09 cases, there was limited clinical information to analyse the underlying cause for weight decrease. Hence, this event is not considered as a safety concern as of now.
Chest pain	28-Jan-19	Database	Yes	No	4	3	30	34	This is a listed event.
Eczema	28-Jan-19	Database	No	No	0	0	2	2	Overall 02 cases of eczema reported with Endari till date and the event was assessed as non-serious in all the case. There was limited information in all the cases and hence this is not considered as a signal at this moment, but a continuous monitoring will be performed to further evaluate this event. Note: The event met the frequency of 03 on 29 Jan 2019. However as per current frequency, the case count is 02.
Gastroenteritis viral	28-Jan-19	Database	No	No	0	2	7	7	Overall 07 cases of viral gastroenteritis were reported with Endari till date and the event was assessed as non-serious in all the cases. In view of limited clinical details for assessment of all the cases, and considering that such infections are common in patients with sickle cell disease, this event is not considered as a safety concern as of now.
Hypotension	28-Jan-19	Database	No	No	1	1	6	7	Overall 07 cases of hypotension were reported with Endari till date. The event was assessed as serious in 01 case requiring hospitalization and non-serious in 06 cases. In 01 case, the event was resolving upon reducing the dose of Endari while in 01 case, the event can be explained by associated dehydration. 01 case had limited information and in 03 cases, the event had a plausible temporal relationship; however, details of medical history and concomitant medications are limited for a proper case assessment. In the last 01 case, the event was a complication to underlying sickle cell disease. Hence, this event is not considered as a safety concern as of now.
Influenza	28-Jan-19	Database	No	No	8	10	14	23	Overall 23 cases of influenza reported till date while the patient was on Endari. The event was serious in 11 cases requiring hospitalization and the event was non-serious in remaining 12 cases. Considering that infections such as influenza is an expected occurrence in patients of sickle cell disease, this is not considered as a safety concern as of now.
Nasopharyngitis	28-Jan-19	Database	No	No	2	4	10	12	Overall 12 cases of Nasopharyngitis were reported till date and all the cases were non-serious. Information was limited in all the cases and also considering that infections are not uncommon in patients with underlying sickle cell disease, this event is not considered as a safety concern as of now.
Pain in extremity	28-Jan-19	Database	Yes	No	14	8	26	40	This is a listed event.

Pneumonia/Pneumonia influenzal/Pneumonia bacterial	28-Jan-19	Database	No	No	4	16	24	27	Note: As per the FR there are 28 cases of pneumonia; however in 01 case, the event was coded twice. So the total cases are 27 inclusive of PT's pneumonia, pneumonia influenzal and pneumonia bacterial reported with Endari. Of the 27 cases, 19 cases were serious requiring hospitalization while remaining 08 were non-serious. Considering that infections such as pneumonia is common in patients with underlying sickle cell disease, this event is not considered as a safety concern as of now.
Rash	28-Jan-19	Database	No	No	0	4	10	10	Overall 10 cases of rash have been reported with Endari till date and the event was non-serious in all the cases. In 01 case, there was temporal association between the onset of rash and therapy with Endari; Endari was discontinued however the outcome is unknown. In the remaining 09 cases there was limited clinical information. Hence, this event is not considered as a safety concern as of now.
Abdominal distension	17-Apr-19	Database	No	No	0	9	13	13	Overall 13 cases were reported with endari till date and the event was assessed as serious in 01 case and non-serious in 12 cases. Of the 13 cases, In 03 cases de-challenge was positive; in 02 cases, the temporal association was clearly mentioned, in 06 cases, there was limited clinical details for assessment of the event and inremaining 02 cases, the event could be confounded by associated event of constipation. As per the PI, abdominal pain is a lablelled event and in view of these facts, this event is not considered as a signal at this moment, but a continuous monitoring will be performed to further evaluate this event as a signal.
Adverse drug reaction (inc. adverse event)	17-Apr-19	Database	Yes	No	14	13	129	144	This is a listed event.
Condition aggravated	17-Apr-19	Database	No	No	0	3	27	27	Overall 27 cases with 31 events of condition aggravated (PT condition aggravated coded thrice in EMM201805-000167 and EMM201806-000249, hence total case count is 27 and event count is 31) were reported with Endari till date. 17 cases were serious while rest were non-serious. Of the 27 case reports, in 20 cases, the event was presumably associated with underlying condition of sickle cell disease and in 06 events there was no information available regarding underlying medical condition. In the last 01 case , there was aggravation of underlying diabetes mellitus and sickle cell disease. In view of these facts, this event is not considered as a safety concern as of now.
Drug ineffective (inc. therapeutic response shortened/Therapeutic response delayed)	17-Apr-19	Database	Yes	No	1	7	18	20	Overall 20 cases including 19 cases of drug ineffective and 1 case of therapeutic response shortened reported with Endari till date. All the cases were non-serious. Out of 20 cases, in 13 cases, LOE was clinically not evident and in 06 cases LOE was clinically evident. All the 06 clinically evident cases, there was inadequate information. The last 01 case was a composite literature report with overlapping information and excluded from analysis. No lot number or batch number were available in any of the cases. Hence, there is no need for further evaluation at this time.
Drug intolerance	17-Apr-19	Database	Yes	No	0	0	6	6	This is a listed event.
Incorrect dose administered	17-Apr-19	Database	Yes	No	0	2	10	10	There were 10 cases of incorrect dose administered. The event was non-serious in all the cases. Of all the cases, in 03 cases there was specific information about incorrect dose (15/10 grams once daily, 5 grams twice daily) while in the remaining 07 cases, there was no specific information regarding incorrect dosage. Also, in all the cases, patients experiened multiple AEs like sickle cell anaemia crisis, depression, pruritus, hyperhidrosis, cellulitis etc, however all those AEs were attributed to underlying medical conditions or associated event. Therefore event was not considred as safety concern as of now.
Medication error	17-Apr-19	Database	Yes	No	0	2	24	24	Overall 24 cases of medication error were reported with Endari till date. The event was non-serious in all the cases. Of all the cases, in 10 cases, there was specific information regarding medication error (patients taking 2-3 doses a week, taking 15 gm twice daily with OTC drugs, taking 10 gm twice daily, taking 5 gm twice daily, taking 5 gm in morning, taking once a day and taking 10 gm at night and took all the medication at once) while in remaining 14 cases, it was stated that the patients were not taking endari as prescribed and there was no specific information about the medication error. Also, in all these cases, patients experienced multiple AEs like sickle cell anaemia crisis (4 cases), jaw pain, back pain, ankle injury, wound infection, sepsis, respiratory failure, death, coagulopathy etc, however all those AEs were attributed to underlying medical conditions or associated events. Therefore no further action is required.
Product dose omission	17-Apr-19	Database	Yes	No	27	78	373	402	This is a listed event.
Sickle cell anaemia/Sickle cell anaemia with crisis/Sickle cell disease	17-Apr-19	Database	Yes	No	54	82	426	483	This is a listed event.
Therapy Cessation	17-Apr-19	Database	Yes	No	1	6	13	14	This is a listed event.
Underdose	17-Apr-19	Database	Yes	No	0	6	55	55	Note: There are 55 cases of underdose as per the FR (DLP: 06JAN2020) as compared to 56 cases reported previously beacsue in one case report (EMM201910-000289), the event underdose was recoded to treatment non-compliance. The event was non-serious in all the 55 cases. Of all the cases, in 38 cases, there was specific information regarding underdose (patients taking 5/10 grams twice daily, 5/10/15 grams once daily, mixing 5 grams twice daily, 1/2/half pack per day) while in remaining 17 cases, there was no specific information about underdose. Also, in all these cases, patients experienced multiple AEs like sickle anaemia crisis, death, back pain, leg pain, pruritus, swelling, dysgeusia, haematemesis etc, however all those AEs were attributed to underlying medical conditions or associated events or concomitant medications. Therefore no further action is required.
Arthralgia	6-Jul-19	Database	No	No	10	4	10	19	Overall 19 cases with 20 events of arthralgia were reported with Endari till date (note: event was coded twice in EMM202002-000113, therefore total case count is 19 and event count is 20). The event was serious in 02 case and non-serious in 17 cases. In 02 cases, the event was confounded by concomitant medication like mometasone; in 01 case, event was confounded by fall, in 02 case the event could be attributed to medical history of hip necrosis and underlying sickle cell disease. In 01 case, the event resolved on reducing the dose of endari and in the remaining 13 cases there was limited clinical information to assess causality. Considering the fact that arthralgia is an expected occurrence in patients with underlying sickle cell disease, this event is not considered as a safety concern as of now.

Dizziness	6-Jul-19	Database	No	No	1	5	9	10	Overall 10 cases of dizziness were reported with Endari till date. The event was serious in 01 case and non-serious in the remaining 09 cases. In 01 case, there was temporal relationship between drug and event and in 01 case the event was attributed to concomitant medication of levetiracetam. In the remaining 08 cases there was limited clinical information to assess causality. This event is not considered as a safety concern as of now.
Transfusion	6-Jul-19	Database	No	No	0	1	6	6	Overall 06 cases of transfusion were reported with Endari till date and the event was assessed as serious in 05 cases and non-serious in 01 case. In 01 case, transfusion was done for underlying sickle cell anemia and in the remaining 05 cases there was limited information regarding indication of transfusion. Based on available information and considering the nature of event, the event was not considered as a safety concern as of now.
Death	6-Oct-19	Database	No	No	2	8	11	13	Overall 13 cases of death reported with Endari till date. In 01 case, the event death ocured due to associated events of sepsis, sickle cell anaemia crisis, coagulopathy etc while in the remaining 12 cases, the cause of death was unknown. considering the fact that death rate is higher in patient of sickel cell anemia, the event death is not considered as a safety concern as of now.
Muscle spasms	6-Oct-19	Database	No	No	0	5	4	4	Overall 04 cases with 06 events (PT muscle spasm is coded twice in EMM201902-000054 and EMM201909-000264, therefore total case count is 04 and event count is 6) of muscle spasm were reported with Endari and the event was non-serious in all the cases. In 01 case, there was positive dechallenge while in the remaining 03 cases, there was limited information precluding further assessment. Hence, the event is not considered as a safety concern as of now.
Decreased appetite	6-Jan-20	Database	No	No	0	5	8	8	Overall 08 cases of decreased appetite were reported till date and the event was non-serious in all the cases. Of the 08 cases in 01 case, the dechallenge was positive; in 01 case the event can be explained by underlying motion sickness; 02 cases the event can be explained by underlying sickle cell disease. In the remaining 04 cases, the information was limited for a proper case assessment. The event was not considered as a safety concern as of now.
Cough	17-Apr-20	Database	Yes	No	4	0	3	7	This is a listed event.
Insomnia	17-Apr-20	Database	No	No	3	1	3	6	Overall 06 cases were reported with endari till date and the event was assessed as serious in 01 case and non-serious in the remaining 05 cases. In 01 case, the dechallenge was positive; in 01 case, the event can be explained by the associated event of pain while in the remaining 04 cases, there was limited information precluding further assessment. The event was not considered as a safety concern as of now.