

Dimethyl fumarate and alopecia

Introduction

Dimethyl fumarate is an immunomodulating agent that is used in *the treatment of plaque psoriasis* (Skilarence®) and *relapsing remitting multiple sclerosis* (Tecfidera®)[1,2]. Dimethyl fumarate has been shown to activate the nuclear factor erythroid-derived 2-like (Nrf2) pathway by glutathione depletion. The Nrf2 pathway is a protective pathway against oxidative damage [3]. In plaque psoriasis, reduced glutathione depletion in cells that are involved in psoriasis pathogenesis leads to inhibition of pro-inflammatory cytokine production, decreased inflammatory infiltrate in psoriatic plaques by induction of pro-apoptotic events, inhibition of keratinocyte proliferation and reduced expression of adhesion molecules. In multiple sclerosis, the exact mechanism for the therapeutic effect remains unknown but dimethyl fumarate has been demonstrated to decrease immune cell activation and pro-inflammatory cytokine release in multiple sclerosis patients. Skilarence® was granted market authorisation in 2017 and Tecfidera® was granted market authorisation in 2014. Dimethyl fumarate had been available as non-registered compound drug before market authorisation.

Drugs can affect two phases of the hair follicle cycle: the growth phase (anagen) and the resting phase (telogen) [4]. Alopecia caused by drugs affecting the anagen phase can occur within days to weeks after start. Alopecia caused by telogen interference usually appears 2 to 4 months after start. Drug-induced alopecia usually improves after drug withdrawal, especially when alopecia is caused by telogen interference. Many other factors can cause alopecia, such as nutrition, stress and thyroid disorders [5].

Reports

Between 2 November 2006 and 11 June 2020 the Netherlands Pharmacovigilance Centre Lareb received 92 reports of HLT alopecias associated with the use of dimethyl fumarate (Appendix 1.). A remarkable increase of reports was noticed in the last three years (Fig. 1).

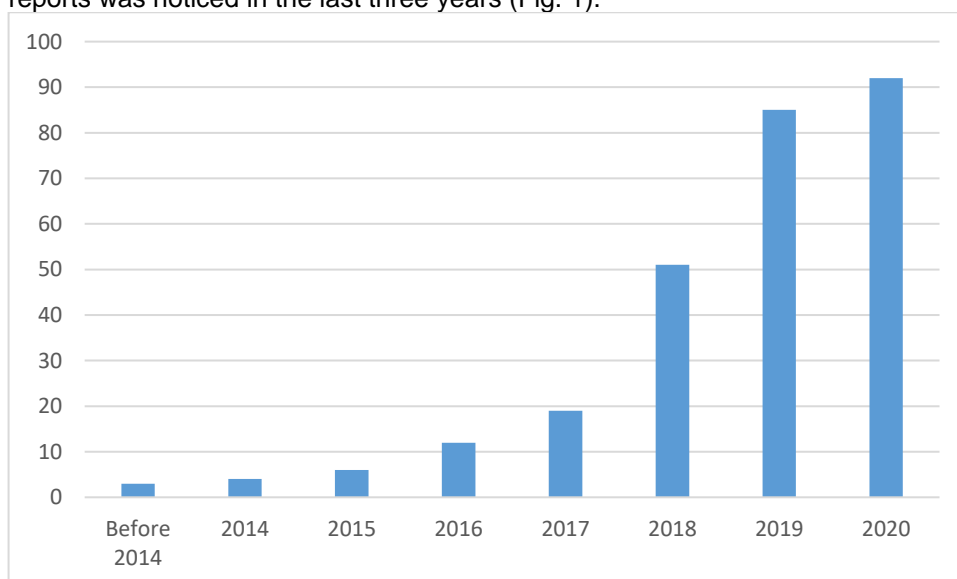


Figure 1. Cumulative number of reports per year concerning HLT alopecias with use of dimethyl fumarate in the Lareb database.

Out of 92 reports, 21 were spontaneously reported to Lareb and 71 were reports received via Marketing Authorization Holders (MAHs). Most reports (82 reports) concerned Tecfidera® and two reports concerned Psorinovo®, a non-registered dimethyl fumarate product that is compounded by Infinity Pharma. The brand name of dimethyl fumarate in the other eight reports is unknown. The reports concerned 81 female and 11 male patients, with a mean age of 40 years (range: 19 to 74 years). Dimethyl fumarate was used for multiple sclerosis in 84 reports (91%), for psoriasis in six reports (7%) and the indication was unknown in two reports. In all reports alopecia was described as hair loss or hair thinning and no description of alopecia areata was reported, although few reports do describe alopecia on other parts of the body than the scalp, such as the eyebrows. In three cases nail issues were also reported adverse drug reactions .

A positive rechallenge was described in one case and a positive dechallenge was reported in 13 cases and recovery after dose reduction was described in one report. In 54 reports (59%) the dose of dimethyl fumarate

was not changed and the patient had not recovered at the moment of reporting. Time to onset varied but was mostly several weeks up to months after start, with a median of 61 days (IQR: 21-122 days). Treatment was described in four reports: vitamin B in one report, a 3- or 5-day methylprednisolone course in two reports (in one of these cases an MS relapse was reported) and unknown treatment in one report.

Some reports are highlighted below:

1. NL-LRB-61336 – A 40-50 year old female patient using dimethyl fumarate for psoriasis experienced hair loss 3 months after start and was recovering 1.5 month after dimethyl fumarate was withdrawn. This patient also had low vitamin B12 levels. The report does not mention treatment of the vitamin B12 levels. The case was reported by a dermatologist.
2. NL-LRB-00286395 – A 40-50 year old female patient using dimethyl fumarate for multiple sclerosis had alopecia 4 months after start which recovered spontaneously while continuing with dimethyl fumarate (without treatment) after 4 to 5 months. Other causes such as vitamin deficiency, iron deficiency and thyroid disorders were excluded by laboratory investigation.
3. NL-LRB-00359969 – A 40-50 year old female patient experienced diffuse hair loss 4 weeks after start with dimethyl fumarate for multiple sclerosis. Dimethyl fumarate was continued and after 10 months, the patient had not recovered and had lost 50% of her hair.
4. NL-LRB-85990 – A 60-70 year old male patient using dimethyl fumarate for psoriasis vulgaris experienced alopecia (and leucopenia) 8 weeks after start. Dimethyl fumarate was withdrawn and the patient recovered 5 months after withdrawal. This case was reported by a specialist doctor.

Other databases

Databases

Table 1. Reports of the PT alopecia associated with dimethyl fumarate in the Lareb, Eudravigilance [6] and WHO database [7].

Database	Drug	Meddra PT	Number of reports	ROR (95% CI)
Lareb	Dimethyl fumarate	Alopecia	81 ^a	1.62 (1.3-2.0)
Eudravigilance	Dimethyl fumarate	Alopecia	335	3.01 (2.7-3.35)
WHO	Fumaric acid	Alopecia	2465	2.7 (2.6-2.8)

- a. The number of reports is lower than the total number of reports received by Lareb because 1.) the ROR calculation is based on PT alopecia while the case assessment is based on HLT alopecias and 2.) reports were registered for different dimethyl fumarate products while ROR calculation was based on reports of one dimethylfumarate product with ATC code: L04AX07.

Prescription data

Table 2. Number of patients using dimethyl fumarate (Tecfidera®) in the Netherlands between 2014 and 2018 according to the GIP database [8]. Prescription data of Skilarence® and non-registered compound drugs was not available.

	2014	2015	2016	2017	2018
Tecfidera®	835	1,897	2,191	2,561	3,059

Literature

Alopecia in a 55 year old woman during dimethyl fumarate treatment for multiple sclerosis has been described in one case report [9]. Alopecia was first noticed 3 months after start and no other cause was found in lifestyle, dermatologic and blood investigations or clinical and medical history. After two months, alopecia slowed down spontaneously and hair growth returned.

On the contrary, alopecia areata has also been associated with multiple sclerosis [10]. Fumaric acid esters have also been shown as effective treatment of alopecia areata in six out of 13 treated patients [11]. However, fumaric acid esters seemed mostly effective in patients with alopecia areata multilocularis and not in alopecia areata totalis or universalis.

Mechanism

A correlation has been demonstrated between the up-regulation of Nrf2 (which is involved in the mechanism of action of dimethyl fumarate) and dilatation of the hair follicle which can result in hair loss during the transitional (catagen) and resting phase of the hair [9,12]. Dimethyl fumarate may also cause alopecia by a direct cytotoxic

effect. This effect may be caused by conjugation of dimethyl fumarate with glutathione which can lead to intracellular glutathione depletion [3].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb has received 92 cases of alopecia in relatively young patients using dimethyl fumarate. Most reports were from MAH's and most reports were received in the last 2 years, which is possibly also related to the increase in number of patients using dimethyl fumarate. Alopecia is not described in the Dutch SmPCs of dimethyl fumarate containing products. Dimethyl fumarate was continued in most cases and most patients had not recovered from alopecia. Time to onset varied from several weeks up to months after start. The association between dimethyl fumarate is disproportionate in the Lareb, Eudravigilance and WHO databases.

Dimethyl fumarate activates the Nrf2 pathway which possibly leads to dilatation of hair follicles and hair loss during the catagen and telogen phase, which is in line with the time to onset in most reports received by Lareb. Even though alopecia areata has been described in patients with multiple sclerosis and dimethyl fumarate has even been demonstrated as treatment of alopecia areata, most of the reports received by Lareb concern diffuse alopecia and not alopecia areata.

Attention to alopecia as an adverse drug reaction of dimethyl fumarate is warranted.

References

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2. Dutch Summary of Product Characteristics Tecfidera®.
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This signal has been raised on August 26, 2020. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbq-meb.nl

Appendix 1. Overview of reports with alopecia related to dimethyl fumarate

	ID, sex, age, primary source	Drug	Dosage	Indication	Concomitant medication	Reported ADRs (Lower Level Term)	Latency after start	Action taken	Outcome
1	NL-LRB-85990, male, 60-70 Years, Physician	Dimethylfumaraat	1 dosage form / 1 Days	Psoriasis vulgaris		Alopecia, Leucopenia	8 Weeks	Drug Withdrawn	Recovered, Recovered
2	NL-LRB-61336, female, 40-50 Years, Physician	Dimethylfumaraat	6 dosage form / Days	Psoriasis		Alopecia	3 Months	Drug Withdrawn	Recovering
3	NL-LRB-239037, male, 50-60 Years, Consumer	Tecfidera Capsule Msr 240Mg	480 mg / 1 Days	Multiple sclerosis		Alopecia universalis	18 Months	Dose Not Changed	Not Recovered
4	NL-LRB-230990, female, 20-30 Years, Physician	Tecfidera Capsule Msr 120Mg	1 dosage form /	Multiple sclerosis		Alopecia	1 Months	Drug Withdrawn	Recovering
5	NL-LRB-230369, female, 40-50 Years, Other health professional	Tecfidera Capsule Msr 240Mg	480 mg / 1 Days	Multiple sclerosis	levothyroxine, acetylsalicylic acid	Alopecia	3 Months	Dose Not Changed	Not Recovered
6	NL-LRB-230061, female, unknown age, Pharmacist	Dimethylfumaraat Psorinovo Tablet Msr Mva 120Mg Ip	720 mg / 1 Days	Drug use for unknown indication		Alopecia	8 Months	Unknown	Unknown
7	NL-LRB-224941, male, 40-50 Years, Physician	Dimethylfumaraat	2 dosage form / 1 Days	Multiple sclerosis	colecalfiferol	Hair loss	14 Months	Drug Withdrawn	Not Recovered
8	NL-LRB-213728, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	480 mg / 1 Days	Multiple sclerosis	bupropion, lithium, levothyroxine	Alopecia, Hair thinning	2 Months, 2 Months	Dose Not Changed	Not Recovered, Not Recovered
9	NL-LRB-193671, female, 60-70 Years, Physician	Dimethylfumaraat	215 mg /	Psoriasis		Hair loss	4 Months	Dose Reduced	Not Recovered
10	NL-LRB-189397, female, 70 Years and older, Pharmacist	Dimethylfumaraat Psorinovo Tablet Msr Mva 120Mg Ip	240 mg / 1 Days	Psoriasis		Eyebrow loss of	4 Years	Dose Reduced	Not Recovered
11	NL-LRB-181768, female, 10-20 Years, Pharmacist	Tecfidera Capsule Msr 120Mg	2 dosage form / 1 Days	Multiple sclerosis		Hair loss	2 Months	Dose Not Changed	Not Recovered
12	NL-LRB-152235, female, 70 Years and older, Pharmacist	Dimethylfumaraat Tab Msr + Mga 120Mg	360 mg / 1 Days	Psoriasis		Alopecia, Brittle nails	2 Weeks	Drug Withdrawn	Recovering, Recovering
13	NL-LRB-00396660, female, 20-30 years, Consumer	Dimethylfumaraat Capsule Msr 240Mg	240 mg / 12 Hours	Multiple sclerosis		Alopecia, Hair breakage	3 Weeks, 3 Weeks	Dose Not Changed	Not Recovered, Not Recovered
14	NL-LRB-00382393, female, 30-40 Years, Physician	Dimethylfumaraat	/	Drug use for unknown indication		Alopecia	3 Months	Unknown	Recovered with squelae
15	NL-LRB-00368225, male, 50-60 Years, Pharmacist	Dimethylfumaraat Tablet Msr 120Mg	240 mg / 12 Hours	Psoriasis		Erectile dysfunction, Body hair loss	4 Weeks	Drug Withdrawn	Not Recovered, Not Recovered

16	NL-LRB-00365751, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 12 Hours	Multiple sclerosis	carbasalate calcium, pantoprazole	Hair loss	1 Month	Dose Not Changed	Not Recovered
17	NL-LRB-00359969, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 12 Hours	Multiple sclerosis		Hair loss	4 Weeks	Dose Not Changed	Not Recovered
18	NL-LRB-00356671, female, 40-50 Years, Physician	Tecfidera Capsule Msr 120Mg	480 mg /	Multiple sclerosis	pantoprazole, baclofen, acetylsalicylic acid, colexaliferol	Hair loss	4 Weeks	Dose Not Changed	Not Recovered
19	NL-LRB-00331241, male, 30-40 years, Other health professional	Tecfidera Capsule Msr 240Mg	240 mg / 12 Hours	Multiple sclerosis	amitriptyline	Hair loss	1 Months	Dose Not Changed	Recovering
20	NL-LRB-00312650, female, 30-40 years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 12 Hours	Multiple sclerosis		Alopecia	4 Months	Dose Not Changed	Not Recovered
21	NL-LRB-00286395, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 12 Hours	Multiple sclerosis	paracetamol, zolmitriptan, baclofen, levocetirizine, metoprolol	Alopecia, unspecified, Erythema, Rhinorrhoea, Gastrointestinal discomfort, Pruritus	4 Months	Dose Not Changed	Recovered, Not Recovered, Recovering, Recovered, Not Recovered
22	NL-BIOGEN-2020BI00876711, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg,	240 mg / 1 Days	Multiple sclerosis		Hair loss, Underdose	62 Days	Dose Not Changed	Not Recovered, Unknown
23	NL-BIOGEN-2020BI00865665, female, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days	Multiple sclerosis		Itch, Hair loss, Flushing	509 Days	Drug Withdrawn	Recovered, Recovered, Recovered
24	NL-BIOGEN-2020BI00858432, female, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	58 Days	Dose Not Changed	Not Recovered
25	NL-BIOGEN-2020BI00828048, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	1 Months	Dose Not Changed	Not Recovered
26	NL-BIOGEN-2020BI00825565, female, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	120 mg / 1 Days, 240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss, Headache, Flushing, Flush hot, Heaviness in leg, Weakness generalized		Dose Not Changed	Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered
27	NL-BIOGEN-2019BI00819818, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair breakage, Hair thinning	214 Days, 214 days	Dose Not Changed	Not Recovered, Not Recovered

28	NL-BIOGEN-2019BI00810773, female, 50-60 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss		Dose Not Changed	Not Recovered
29	NL-BIOGEN-2019BI00800960, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	6 Months	Dose Not Changed	Not Recovered
30	NL-BIOGEN-2019BI00797524, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Flushing, Hair loss, Diarrhea	4 Years	Drug Withdrawn	Recovered, Recovered, Recovered
31	NL-BIOGEN-2019BI00797128, female, 30-40 Years, Other health professional	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis	clemastine, cetirizine	Hair loss, Shortness of breath, Itch, Erythropapular rash, Angioedema		Dose Not Changed	Not Recovered, Not Recovered, Unknown, Unknown, Not Recovered
32	NL-BIOGEN-2019BI00796563, female, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	16 Days	Dose Not Changed	Not Recovered
33	NL-BIOGEN-2019BI00790532, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	131 Days	Dose Not Changed	Not Recovered
34	NL-BIOGEN-2019BI00790497, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	40 Days	Dose Not Changed	Not Recovered
35	NL-BIOGEN-2019BI00789681, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss, Tiredness, Difficulty in walking, Underdose	58 Days	Drug Withdrawn	Recovered, Recovered, Recovered, Recovered
36	NL-BIOGEN-2019BI00787779, female, unknown age, Other health professional	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis		Hair loss, Broken nails		Dose Not Changed	Not Recovered, Unknown
37	NL-BIOGEN-2019BI00787439, female, unknown age, Other health professional	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis		Hair loss		Dose Not Changed	Not Recovered
38	NL-BIOGEN-2019BI00787063, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss, Gastric disorder, Prescribed underdose	75 Days	Dose Not Changed	Not Recovered, Not Recovered, Recovered
39	NL-BIOGEN-2019BI00783772, female, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss, Nail injury	106 Days	Dose Not Changed	Not Recovered, Not Recovered
40	NL-BIOGEN-2019BI00779207, female, , Consumer	Tecfidera Capsule Msr 240Mg		Multiple sclerosis		Hair loss		Dose Not Changed	Not Recovered

41	NL-BIOGEN-2019BI00776850, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Headache, Flushing, Hair loss, Itch	73 days	Dose Not Changed	Not Recovered, Not Recovered, Not Recovered, Unknown
42	NL-BIOGEN-2019BI00770534, male, 50-60 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss, Difficulty in walking, Muscle weakness lower limb	75 Days	Dose Not Changed	Not Recovered, Not Recovered, Not Recovered
43	NL-BIOGEN-2019BI00769138, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	46 Days	Dose Not Changed	Not Recovered
44	NL-BIOGEN-2019BI00768169, female, 50-60 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	82 Days	Dose Not Changed	Not Recovered
45	NL-BIOGEN-2019BI00757300, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Nausea, Dizziness, Pain back, Cramps, Tingling, Flu symptoms, Tiredness, Hair loss		Dose Not Changed	Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered
46	NL-BIOGEN-2019BI00736436, male, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss, Diarrhea		Drug Withdrawn	Recovered, Recovered
47	NL-BIOGEN-2019BI00736415, female, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days	Multiple sclerosis		Hair loss	15 Days	Dose Not Changed	Not Recovered
48	NL-BIOGEN-2019BI00732900, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Weight decrease, Flushing, Diarrhea, Hair loss		Drug Withdrawn	Recovered, Recovered, Recovered, Recovered
49	NL-BIOGEN-2019BI00725385, female, 70 years and older, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	151 Days	Dose Not Changed	Not Recovered
50	NL-BIOGEN-2019BI00724268, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	31 Days 31 Days 31 Days	Dose Not Changed	Not Recovered
51	NL-BIOGEN-2019BI00717752, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Redness, Hair loss, Headache	508 Days	Drug Withdrawn	Recovered, Recovered, Recovered

52	NL-BIOGEN-2019BI00717498, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 120 mg / 1 Days	Multiple sclerosis		Flushing, Restless legs, Insomnia, Forgetfulness, Dizziness, Feeling down, Fatigue, Nerve pain, Hair loss, Dysgeusia	75 Days	Dose Not Changed	Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered
53	NL-BIOGEN-2019BI00713612, female, 50-60 Years, Consumer	Tecfidera Capsule Msr 240Mg	120 mg / 1 Days	Multiple sclerosis		Flushing, Hair loss		Drug Withdrawn	Recovered, Recovered
54	NL-BIOGEN-2019BI00712813, female, 40-50 Years, Other health professional, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis	salbutamol, metoprolol	Diarrhea, Eyelid burning sensation, Eyelids itchy sensation of, Burning sensation in eye, Flushing, Flu, Feeling sick, Hair loss, Flatulence	112 Days	Dose Not Changed	Not Recovered, Not Recovered, Not Recovered, Unknown, Not Recovered, Not Recovered, Recovered, Not Recovered, Not Recovered
55	NL-BIOGEN-2019BI00682834, female, unknown age, Consumer	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis	Vitamin B complex	Accelerated hair loss		Dose Not Changed	Unknown
56	NL-BIOGEN-2019BI00679007, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days	Multiple sclerosis		Stomach ache, Eating disorder, Flu, Hair loss, Diarrhea, Gastric disorder	18 Days	Dose Not Changed	Recovered, Not Recovered, Recovered, Not Recovered, Not Recovered, Not Recovered
57	NL-BIOGEN-2019BI00678243, female, unknown age, Other health professional	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis		Hair loss		Unknown	Unknown
58	NL-BIOGEN-2019BI00678147, female, unknown age, Other health professional	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis		Hair loss		Dose Not Changed	Not Recovered

59	NL-BIOGEN-2018BI00671275, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days	Multiple sclerosis		Hair loss, Weight gain, Shortness of breath, Dizziness, Nausea, Swelling face	1 Days	Dose Not Changed	Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered
60	NL-BIOGEN-2018BI00663166, female, 50-60 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss, Underdose	4 Months	Dose Not Changed	Not Recovered, Unknown
61	NL-BIOGEN-2018BI00658825, female, unknown age, Consumer	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis		Flushing, Tiredness, Physical deconditioning, Hair loss		Dose Not Changed	Not Recovered, Recovered, Not Recovered, Unknown
62	NL-BIOGEN-2018BI00655596, female, unknown age, Consumer	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis		Bladder inflammation, Hair loss, Sinusitis		Drug Withdrawn	Not Recovered, Not Recovered, Not Recovered
63	NL-BIOGEN-2018BI00653775, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	< 1 day	Drug Withdrawn	Not Recovered
64	NL-BIOGEN-2018BI00651254, female, 50-60 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss, Off label use, Feeling sad	32 days	Drug Withdrawn	Recovered, Unknown, Recovered
65	NL-BIOGEN-2018BI00642386, female, , Other health professional	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis		Hair loss	-	Unknown	Not Recovered
66	NL-BIOGEN-2018BI00637113, female, 30-40 Years, Other health professional	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis		Alopecia	-	Unknown	Unknown
67	NL-BIOGEN-2018BI00636567, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days	Multiple sclerosis		Flushing, Hair loss, MS aggravated		Dose Not Changed	Not Recovered, Not Recovered, Not Recovered
68	NL-BIOGEN-2018BI00635182, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days	Multiple sclerosis		Hair loss	7 Days	Drug Withdrawn	Not Recovered
69	NL-BIOGEN-2018BI00631569, female, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Flushing, Hair loss		Drug Withdrawn	Not Recovered, Not Recovered
70	NL-BIOGEN-2018BI00630025, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss, Prescribed underdose	127 Days	Dose Not Changed	Not Recovered, Recovered

71	NL-BIOGEN-2018BI00616807, male, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days	Multiple sclerosis		Hot flush, Air in intestines, Prescribed underdose, Hair loss, Flushing	11 Days	Dose Not Changed	Not Recovered, Not Recovered, Unknown, Not Recovered, Not Recovered
72	NL-BIOGEN-2018BI00616806, male, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss, Sleep problem, Pain neck, Fever, Back disorder		Dose Not Changed	Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered
73	NL-BIOGEN-2018BI00614381, female, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	14 Days	Dose Not Changed	Not Recovered
74	NL-BIOGEN-2018BI00604731, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	70 Days	Dose Not Changed	Not Recovered
75	NL-BIOGEN-2018BI00604414, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss, Tiredness, Night sweats		Drug Withdrawn	Not Recovered, Not Recovered, Not Recovered
76	NL-BIOGEN-2018BI00595695, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days	Multiple sclerosis		Hair loss	10 Days	Dose Not Changed	Not Recovered
77	NL-BIOGEN-2018BI00587508, female, unknown age, Consumer	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis		Multiple sclerosis relapse, Folic acid decreased, Hair loss, Painful joints, Tiredness, Poor sleep, Paresthesia aggravated		Unknown	Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered
78	NL-BIOGEN-2018BI00584840, female, 30-40 Years, Other health professional	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis		Alopecia	436 Days	Dose Not Changed	Not Recovered
79	NL-BIOGEN-2018BI00559448, male, unknown age, Consumer	Tecfidera Capsule Msr 240Mg	/	Multiple sclerosis		Itchy rash, Hair loss, Micturition disorder, Multiple sclerosis	87 Days	Dose Not Changed	Not Recovered, Not Recovered, Not Recovered, Not Recovered

80	NL-BIOGEN-2018BI00553799, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Multiple sclerosis relapse, Hair loss	71 Days	Dose Not Changed	Not Recovered, Not Recovered
81	NL-BIOGEN-2018BI00539858, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	346 Days	Dose Not Changed	Not Recovered
82	NL-BIOGEN-2018BI00536922, male, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	31 Days	Dose Not Changed	Recovered
83	NL-BIOGEN-2018BI00527422, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 120 mg / 1 Days	Multiple sclerosis		Stomach pain, Diarrhea, Feeling sick, Feeling hot and cold, Intentional underdose, Mood swings, Menstruation prolonged, Gastrointestinal symptom NOS, Hair loss	258 Days	Dose Reduced	Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Recovered, Recovered
84	NL-BIOGEN-2018BI00522811, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss		Dose Not Changed	Not Recovered
85	NL-BIOGEN-2018BI00518592, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 120 mg / 1 Days	Multiple sclerosis		Pain stomach, Hair loss	15 Days	Dose Reduced	Not Recovered, Not Recovered
86	NL-BIOGEN-2017BI00501993, female, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis =		Hair loss, Underdose, Gastrointestinal symptom NOS	77 Days	Dose Not Changed	Not Recovered, Recovered, Not Recovered
87	NL-BIOGEN-2017BI00495446, female, , Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days	Multiple sclerosis		Flushing, Gastrointestinal symptom NOS, Hair loss	1 Days	Drug Withdrawn	Recovered, Recovered, Recovered
88	NL-BIOGEN-2017BI00494208, female, 40-50 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days	Multiple sclerosis		Bladder infection, Hair loss, Flushing, Feeling bad, Decreased immune responsiveness, Pyelitis		Drug Withdrawn	Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered
89	NL-BIOGEN-2017BI00474280, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair loss	32 Days	Dose Not Changed	Not Recovered

90	NL-BIOGEN-2017BI00472542, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days	Multiple sclerosis		Nauseous, Vomited, Hot flush, Weakness, Sweating, Hair loss, Underdose, Difficulty in walking	2 Months	Dose Not Changed	Not Recovered, Not Recovered, Not Recovered, Not Recovered, Not Recovered, Unknown, Not Recovered
91	NL-BIOGEN-2017BI00456655, female, 30-40 Years, Consumer	Tecfidera Capsule Msr 240Mg	240 mg / 1 Days, 480 mg / 1 Days	Multiple sclerosis		Hair thinning	178 Days	Dose Not Changed	Recovered
92	NL-BIOGEN-2016BI00232389, female, 20-30 Years, Consumer	Tecfidera Capsule Msr 240Mg	120 mg / 1 Days, 240 mg / 1 Days	Multiple sclerosis		Depression, Hair loss, Flushing, Skin rash, Redness of legs, Intentional misuse in dosing frequency, Mood swings, Bipolar disorder	85 Days	Not Applicable	Not Recovered, Unknown, Not Recovered, Not Recovered, Unknown, Unknown, Not Recovered, Not Recovered