

## *Supplementary Materials for*

# Adverse events related to herbal dietary supplements and over-the-counter medications containing laxatives: a 10-year update from the Italian Phytovigilance and Pharmacovigilance systems

Niccolò Lombardi, Giada Crescioli, Valentina Maggini, Valentina Brilli, Francesca Menniti-Ippolito, Ilaria Ippoliti, Simona Potenza, Francesca Renda, Gabriela Mazzanti, Annabella Vitalone, Alfredo Vannacci and Fabio Firenzuoli

### *Corresponding author:*

Alfredo Vannacci, Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino, Sezione di Farmacologia e Tossicologia, Università degli Studi di Firenze, Viale G. Pieraccini 6, 50139 Florence, Italy.  
E-mail: alfredo.vannacci@unifi.it.

### *Published on*

Ann Ist Super Sanità 2022 Vol. 58, No. 2: 131-138  
DOI: 10.4415/ANN\_22\_02\_09

### *This PDF file includes:*

#### **Supplementary Table 1a**

Suspected adverse events associated with dietary supplements used as laxatives reported to the Italian Phytovigilance system from February 2011 to December 2020

#### **Supplementary Table 1b**

Suspected adverse events related to over-the-counter medications used as laxatives reported to the Italian Pharmacovigilance system from January 2011 to December 2020

### Supplementary Table 1a

Suspected adverse events associated with dietary supplements used as laxatives reported to the Italian Phytovigilance system from February 2011 to December 2020

Age (year)/gender	Components <sup>a</sup> (brand name)	Duration of use/latency <sup>b</sup>	Adverse events	Hospitalization/recovery	Other medications/conditions	Dechallenge/rechallenge	Causality assessment
49/F	Chicory plants, <i>Gentiana lutea</i> (Gentian), <i>Rheum palmatum</i> (Rhubarb) roots, <i>Cassia angustifolia</i> leaves, <i>Aloe vera</i> and <i>Aloe arborescens</i> , <i>Rhamnus frangula</i> , Cinnamon bark, Cloves (VERAVIS-PLUS <sup>c</sup> )	3 years/1 year	<i>Melanosis coli</i>	No/complete	Venlafaxine, ramipril, lithium carbonate/recurrent major depression	Positive/NR	Probable
41/M	Aloe leaves (ALOINA) <sup>c</sup>	NR	Vomiting, epigastric pain, diarrhoea	Yes/complete	NR/gastroesophageal reflux	Positive/NR	Possible
22/M	<i>Cassia angustifolia</i> leaves powder, Dandelion ( <i>Taraxacum officinale</i> ) root powder, Aloe ( <i>Aloe ferox</i> ) leaves juice, Chicory ( <i>Cichorium intybus</i> ) root powder, Fennel ( <i>Foeniculum vulgare</i> ) fruits powder, Caraway ( <i>Carum carvi</i> ) fruits powder, Cumin ( <i>Cuminum cyminum</i> ) fruits powder, Fennel ( <i>Foeniculum vulgare</i> ) essential oil natural flavor (SOLLIEVO TAVOLETTE <sup>c</sup> )	1 day/1 day	Bloody diarrhoea	Yes, access to the emergency room/complete	NR	NR	Probable
49/F	Rhubarb, tamarind, fig (FRUTTA E FIBRE <sup>c</sup> )	NR	Diarrhea, abdominal cramps, fever, intestinal hyperemia, intestinal ulceration	Yes/complete	NR	Positive/NR	Probable
33/M	<i>Cascara sagrada</i> (not otherwise specified)	3 days/3 days	Paralytic ileum, urinary retention	Yes/NR	Other product not otherwise specified/NR	NR	Possible
29/F	24 billion live lactic ferments and psyllium fibre (PSYLLOGEL <sup>c</sup> megafermenti) <sup>d</sup>	NR	Abdominal pain	No/complete	1. Cardioaspirin 2. Folina <sup>e</sup> (folic acid) 3. PRENIUS <sup>e</sup> (L-arginine, magnesium, <i>Salix alba</i> )/NR	Positive/NR	Possible
70/F	<i>Cascara</i> , <i>Aloe vera</i> , Senna, Dandelion (PUNTUALE) <sup>d</sup>	1 year/1 year	Abdominal pain	No/complete	1. paclitaxel 2. trastuzumab/1. appendectomy, appendix-hysterectomy 2. breast cancer	Positive/positive	Possible
62/F	<i>Orthosiphon stamineus</i> dry extract, cassia (not otherwise specified) dry extract, frangula ( <i>Rhamnus frangula</i> ) dry extract, cimicifuga ( <i>Cimicifuga racemosa</i> ) dry extract, tamarind dry extract, L-carnitine, green tea dry extract ( <i>Camellia sinensis</i> ) (KILOCAL <sup>e</sup> )	10 days/10 days	Colic, constipation, diarrhoea	No/complete	1. carbamazepine (since 2015) 2. scopolamine butylbromide (when needed) 3. KILOCAL <sup>e</sup> (Magnolia dry extract, soya dry extract (isoflavones), green tea, inositol, hydrolyzed casein, lemon balm dry extract)/NR	Positive/NR	Possible
32/F	<i>Plantago psyllium</i> , Glucomannan, Lactulose, <i>Cassia</i> (not otherwise specified) <i>angustifolia</i> (herbal extract) (DIMALOSIO <sup>e</sup> )	11 days/11 days	Erythema, dermatitis	Yes/improvement	1. fluconazole 2. enalapril/NR	Positive/NR	Possible
54/F	<i>Cassia angustifolia</i> leaves powder, Dandelion ( <i>Taraxacum officinale</i> ) root powder, Aloe ( <i>Aloe ferox</i> ) leaves juice, Chicory ( <i>Cichorium intybus</i> ) root powder, Fennel ( <i>Foeniculum vulgare</i> ) fruits powder, Caraway ( <i>Carum carvi</i> ) fruits powder, Cumin ( <i>Cuminum cyminum</i> ) fruits powder, Fennel ( <i>Foeniculum vulgare</i> ) essential oil natural flavor (SOLLIEVO BIO TAVOLETTE <sup>c</sup> )	2 days/3 days	Localized erythema	Yes access to the emergency room/improvement	NR/allergy to chlorine, iodine, aspirin, nimesulide, nickel	Positive/NR	Probable

Continues

**Supplementary Table 1a**

Continued

Age (year)/gender	Components* (brand name)	Duration of use/latency <sup>b</sup>	Adverse events	Hospitalization/recovery	Other medications/conditions	Dechallenge/rechallenge	Causality assessment
48/F	<i>Cassia angustifolia</i> leaves and fruits dry extract titrated at 20% in sennosides, <i>Cassia angustifolia</i> leaves and fruits micronized total, <i>Rhamnus frangula</i> dry extract titrated 20% in glucofrangulin (5 mg), plum fruit dry extract titrated 7% in sorbitol, china total micronized bark, chicory root dry extract titrated 90% in inulin (BUONERBE REGOLA FORTE) <sup>c</sup>	NR	Generalized hives rash, edema of the face, angioedema	Yes/complete	NR/allergy to mites	Positive/NR	Probable
28/F	<i>Cassia angustifolia</i> leaves powder, Dandelion ( <i>Taraxacum officinale</i> ) root powder, Aloe ( <i>Aloe ferox</i> ) leaves juice, Chicory ( <i>Cichorium intybus</i> ) root powder, Fennel ( <i>Foeniculum vulgare</i> ) fruits powder, Caraway ( <i>Carum carvi</i> ) fruits powder, Cumin ( <i>Cuminum cyminum</i> ) fruit powder, fennel ( <i>Foeniculum vulgare</i> ) essential oil natural flavor (SOLLIEVO) <sup>c</sup>	1 day/1 day	Lip edema, pre-syncope, hyperaemia, hives rash	Other condition/improvement	1. Ibuprofen 2. BIOTIC <sup>c</sup> (echinacea ( <i>Echinacea purpurea</i> Moench) seeds dry extract, echinacea ( <i>Echinacea angustifolia</i> ) radix dry extract, melaleuca ( <i>Melaleuca alternifolia</i> Cheel) aerial part/NR	NR/	Possible
58/F	Frangula ( <i>Rhamnus frangula</i> L, cortex) dry extract; Senna ( <i>Cassia angustifolia</i> Vahl, folium) dry extract; Green coffee ( <i>Coffea arabica</i> L, semen) dry extract; <i>Coleus forskohlii</i> , radix, dry extract titrated at 10% in forskolin; Guarana ( <i>Paullinia cupana</i> Kunth, semen) dry extract; LeptiCore (high viscosity polysaccharides from Guar gum ( <i>Cyamopsis tetragonolobus</i> L, semen), Carob ( <i>Ceratonia siliqua</i> L, fructus), Acacia gum ( <i>Acacia nilotica</i> Willd Ex Del., Gummi), Pomegranate ( <i>Punica granatum</i> L, fructus) dry extract, Blue alga ( <i>Aphanizomenon flos-aquae</i> , bacteria), beta-carotene, esterified fatty acids); Cassia ( <i>Cassia fistula</i> L, fructus) dry extract; Tamarind ( <i>Tamarindus indica</i> L, fructus) dry extract; (KILOCAL) <sup>c</sup>	NR	Itching, erythema, allergic reaction	Yes/NR	1. diazepam 2. simvastatin 3. paroxetine hydrochloride/NR	NR	Possible
65/F	Malva ( <i>Malva sylvestris</i> L.) leaves fluid extract, green tea ( <i>Camellia sinensis</i> L. Kuntze) leaves fluid extract, ethyl alcohol, aromas, Carvi ( <i>Carum carvi</i> L.) fruit fluid extract, Lemon balm ( <i>Melissa officinalis</i> L.) leaf fluid extract 0,1g, Flax ( <i>Linum usitatissimum</i> L.) seeds fluid extract, Dioscorea ( <i>Dioscorea villosa</i> L.) rhizome fluid extract, Contains celery (PESOFORMA HYDROSLIM) <sup>c</sup>	1 day/1 day	Rash, airway oedema, vomiting, anaphylactoid reaction	Yes/complete	flurazepam monochlorinated/NR	Positive/NR	Probable
59/M <sup>c</sup>	<i>Elianthus annuus</i> , <i>Citrus dulcis</i> , <i>Pinus</i> , <i>Eucalyptus globe</i> , <i>Litsea cubeba</i> , <i>Citrus amara</i> , <i>Citrus limonum</i> , <i>Pinus sylvestris</i> , <i>Pinus mugo</i> , <i>Foeniculum vulgare</i> , Anethole, <i>Mentha piperita</i> , <i>Mentha arvensis</i> , <i>Citrus nobilis</i> , Ferrous, <i>Evernia prunastris</i> , <i>Salvia officinalis</i> , Camphor, Menthol, <i>Cinnamum zeylanicum</i> <sup>c</sup> (OLIO 31) <sup>c</sup>	1 day/1 day	Generalized hives reaction, allergic reaction, difficulty breathing, tongue edema	Yes/NR	NR/asthma	NR	Probable

Continues

**Supplementary Table 1a**

Continued

Age (year)/gender	Components <sup>a</sup> (brand name)	Duration of use/latency <sup>b</sup>	Adverse events	Hospitalization/recovery	Other medications/conditions	Dechallenge/rechallenge	Causality assessment
83/F	<i>Cassia angustifolia</i> leaves (micronized powder), <i>Aloe vera</i> juice (dried micronized powder), <i>Rhamnus purshiana</i> ( <i>Cascara sagrada</i> ) bark (micronized powder), <i>Rheum palmatum</i> (Rhubarb) rhizome (micronized powder), <i>Taraxacum officinale</i> (Dandelion) root (micronized powder), <i>Malva sylvestris</i> (Mallow) flowers and leaves (dry extract), <i>Foeniculum vulgare</i> (Fennel) fruit micronized powder, <i>Glycyrrhiza glabra</i> (Liquorice) root (micronized powder), Clove (micronized powder), <i>Gentiana lutea</i> (Gentian) root (micronized powder) (ERBALAX FLOR <sup>c</sup> )	10 years/10 years	Acute hepatitis	Yes/after sequelae conditions	1. ramipril+hydrochlorothiazide 2. atorvastatin/previous HAV	Positive/NR	Possible
36/M	<i>Aloe vera</i> (ALOE VERA SCIROPPO) <sup>c</sup>	21 days/19 days	Increased transaminase value	No/improvement	NR/recovering from cytomegalovirus hepatitis	Positive/NR	Possible
56/F	Orthosiphon ( <i>Orthosiphon stamineus</i> ) leaves, Rooibos ( <i>Aspalathus linearis</i> ) leaves, Burdock ( <i>Arctium lappa</i> ) root, Liquorice ( <i>Glycyrrhiza glabra</i> ) root, Fennel ( <i>Foeniculum vulgare</i> ) fruits, Star anise ( <i>Illicium verum</i> ) fruits, Artichoke ( <i>Cynara scolymus</i> ) leaves, Aloe ( <i>Aloe vera</i> ) lyophilized leaf gel, Lemon ( <i>Citrus limonum</i> ) essential oil, Peppermint ( <i>Mentha piperita</i> ) essential oil (FISIODEPUR CONCENTRATO FLUIDO) <sup>c</sup>	1 month/27 days	Rhabdomyolysis	Yes/NR	1. Revidox <sup>®</sup> [STILVID: standardized dry extract of Grape peel and seeds ( <i>Vitis vinifera</i> ), dry extract of Garnet fruit ( <i>Punica granatum</i> )] 2. Fish Factor Col <sup>®</sup> (Plant sterol esters, fish oil concentrate in EPA and DHA, corn hydroxypropyl starch, chlorophyll complexes)/Intense upper limb myalgia (after usual sporting activity)	NR	Possible
38/F	Fucus dry extract titrated in 0.1% iodine, sodium levothyroxine, ruscus dry extract titrated in 5% ruscogenin, Senna dry extract titrated in 12% sennosides, <i>Cassia nomame</i> dry extract; Cascara dry extract titrated in 10% cascarosides; paroxetine; spironolactone, chromium picolinate (galenic preparation)	NR	Confusion, disorientation, physical agitation, tachycardia, thyrotoxicosis	Yes/complete	Other product (syneprine tartate, caffeine, glucomannan)/NR	Positive/No	Possible
75/M	<i>Cassia angustifolia</i> , <i>Rhamnus purshiana</i> , <i>Rheum palmatum</i> (Rhubarb), Aloe, Malva, <i>Rhamnus frangula</i> , Bindweed, Carnation and Cinnamon (COTIDIERBE) <sup>c</sup>	NR	Hyperkalemia	Yes/NR	Other product not otherwise specified/NR	NR	Possible
82/M	<i>Cassia angustifolia</i> leaves powder, Dandelion ( <i>Taraxacum officinale</i> ) root powder, Aloe ( <i>Aloe ferox</i> ) leaves juice, Chicory ( <i>Cichorium intybus</i> ) root powder, Fennel ( <i>Foeniculum vulgare</i> ) fruits powder, Caraway ( <i>Carum carvi</i> ) fruits powder, Cumin ( <i>Cuminum cyminum</i> ) fruits powder, Fennel ( <i>Foeniculum vulgare</i> ) essential oil natural flavor (SOLLIEVO BIO TAVOLETTE) <sup>c</sup>	32 days/40 days	Increase in INR	No/complete	1. amiodarone hydrochloride 2. ramipril 3. warfarin 4. simvastatin 5. acetylsalicylic acid/NR	Positive/Positive	Probable

Continues

### Supplementary Table 1a

Continued

Age (year)/gender	Components* (brand name)	Duration of use/latency <sup>b</sup>	Adverse events	Hospitalization/recovery	Other medications/conditions	Dechallenge/rechallenge	Causality assessment
49/M	Tamarind ( <i>Tamarindus indica</i> ), senna ( <i>Cassia angustifolia</i> ), inulin, frangula ( <i>Rhamnus frangula</i> ), <i>Cassia fistula</i> , fruit oligosaccharides, <i>Fucus vesiculosus</i> titrated thallus 0,1% in Iodine, star anise ( <i>Illicium verum</i> ), pineapple ( <i>Bromelia ananas</i> ), chromium picolinate. (KILOCAL <sup>c</sup> )	6 days/6 days	Ischemic stroke	Yes/persistent reaction	No/1. strong smoker 2. hypertension 3. overweight 4. hypercholesterolemia	NR	Possible
72/F	99% pure Psyllium fiber (PSYLLOGEL <sup>c</sup> )	NR	Alopecia, abnormal slimming	No/complete	1. beta blocking agents 2. antihypertensive 3. diuretics 4. cardioaspirin/NR	NR	Possible
59/M <sup>e</sup>	<i>Elianthus annuus</i> , <i>Citrus dulcis</i> , <i>Pinus</i> , <i>Eucalyptus globe</i> , <i>Litsea cubba</i> , <i>Citrus amara</i> , <i>Citrus limonum</i> , <i>Pinus silvestris</i> , <i>Pinus mugo</i> , <i>Foeniculum vulgare</i> , <i>Anethole</i> , <i>Mentha piperita</i> , <i>Mentha arvensis</i> , <i>Citrus nobilis</i> , Ferrous, <i>Evernia prunastris</i> , <i>Salvia officinalis</i> , Camphor, Menthol, <i>Cinnamomum zeylanicum</i> <sup>c</sup> (OLIO 31 <sup>d</sup> )	1 day/1 day	Systemic anaphylactic reaction	Yes/NR	1. salbutamol 2. corticosteroids/allergic asthma	NR	Probable

F: female; HAV: hepatitis A virus; M: male; NR: not reported.

<sup>a</sup> As reported on product label.

<sup>b</sup> Latency = time from the beginning of treatment until the onset of the adverse event.

<sup>c</sup> Herbal product.

<sup>d</sup> The composition information was taken from the internet site.

<sup>e</sup> It is assumed that it is the same subject.

### Supplementary Table 1b

Suspected adverse events related to over-the-counter medications used as laxatives reported to the Italian Pharmacovigilance system from January 2011 to December 2020

Age (year)/gender	Components* (brand name)	Duration of use/latency <sup>b</sup>	Adverse events	Hospitalization/recovery	Other medications/concomitant conditions	Dechallenge/rechallenge	Causality assessment
NR/M	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	NR	Abdominal pain, abdominal cramps	No/NR	NR	NR	NR
68/M	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	2 days/3 days	Epigastric pain	No/improvement	NR/renal colic (2008 and 2013), constipation, Dupuytren's intervention for contracture, politraumatism	NR	NR
79/M	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	1 day/2 days	Diarrhea, feeling of fainting	No/improvement	NR	Positive/NR	NR
83/F	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	1 day/1 day	Diarrhea	No/improvement	NR/bronchitis	NR	NR
71/M	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	1 day/1 day	Abdominal pain, haematuria	No/improvement	NR	NR	NR
65/M	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	NR/8 days	Abdominal pain, epigastric pain	No/NR	NR	NR	NR
84/F	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	1 day/1 day	Abdominal pain, nausea, vomiting	No/complete	NR	Positive/NR	NR
28/F	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	1 day/1 day	Abdominal pain, vomiting	No/improvement	NR/irritable bowel syndrome	NR	NR
87/F	Senna leaf sennosides a and b (X Prep <sup>e</sup> )	1 day/2 days	Vomiting, diarrhea	No/improvement	NR	NR	NR
70/F	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	NR	Heaviness in the stomach	No/NR	NR	NR	NR

Continues

**Supplementary Table 1b**  
Continued

Age (year)/gender	Components* (brand name)	Duration of use/latency <sup>b</sup>	Adverse events	Hospitalization/recovery	Other medications/concomitant conditions	Dechallenge/rechallenge	Causality assessment
46/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/2 days	Abdominal pain	No/improvement	NR	NR	NR
56/M	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	2 days/2 days	Abdominal pain	No/NR	NR	NR	Possible
35/M	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/2 days	Abdominal pain	No/complete	NR	Positive/NR	Possible
55/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/2 days	Abdominal pain, nausea	No/complete	NR	Positive/NR	Possible
32/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/1 day	Abdominal pain, abuse	No/Complete	NR/anxiety, depressive syndrome	NR	NR
47/F	Senna leaf sennosides a and b (X Prep <sup>†</sup> )	1 day/1 day	Abdominal pain, vomiting	No/improvement	NR/surgery for meningioma	Positive/NR	NR
92/M	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	NR	Paralytic ileus	No/NR	NR	Positive/NR	NR
77/F	Senna leaf sennosides a and b (X Prep <sup>†</sup> )	NR	Abdominal pain	No/improvement	1. mesalazine 2. esomeprazole 3. candesartan cilexetil 4. domperidone/chronic constipation	NR	NR
52/M	Senna leaf sennosides a and b (X Prep <sup>†</sup> )	NR/3 days	Constipation	No/improvement	NR	NR	Possible
78/F	<i>Cassia angustifolia</i> , <i>Cassia fistula</i> (Tamarine <sup>®</sup> )	7 years/7 years	Diarrhea, abdominal pain, headache	No/complete	1. neбиволol 2. atorvastatin 3. pantoprazole	Positive/positive	NR
55/M	Neo heparbil <sup>†</sup>	NR	Abdominal pain, headache	No/complete	NR	Positive/NR	NR
39/M	Bisacodile	1 day/1 day	Abdominal pain, agitation, diarrhea, general malaise	No/persistent	NR/ernia in the hiatus	Negative/NR	NR
78/M	Cascara dry extract ( <i>Rhamnus purshiana</i> ) rhubarb dry extract, boldo, dihydroxybutyl ether (DIS CINIL COMPLEX <sup>®</sup> )	1 day/1 day	Epigastralgia, retrosternal pain, retching	No/Complete	NR/chronic gastritis, diabetes mellitus, hypertension, chronic idiopathic constipation	Positive/NR	NR
92/F	Cascara dry extract rhubarb dry extract ( <i>Rhamnus purshiana</i> ), boldo, dihydroxybutyl ether (DIS CINIL COMPLEX <sup>®</sup> )	1 day/2 days	Epigastralgia, headache, arm pain	No/complete	NR	NR	NR
NR/F	<i>Cassia angustifolia</i> , <i>Cassia fistula</i> (Tamarine <sup>®</sup> )	NR	Abdominal pain, vomiting, abnormal smell of the product	No/complete	NR	Positive/NR	NR
NR/F	<i>Cassia angustifolia</i> , <i>Cassia fistula</i> (Tamarine <sup>®</sup> )	NR	Abdominal pain, incomplete pharmacological effect	No/complete	NR/gastrointestinal disorder, constipation, rectocele	NR	NR
62/M	Ispaghula (psyllium seeds) (Agiolax <sup>®</sup> )	NR	Lack of pharmacological effect, solid stools, frequent defecations	No/NR	Olprezide/abnormal blood pressure	NR	Possible
87/F	<i>Cassia angustifolia</i> , <i>Cassia fistula</i> (Tamarine <sup>®</sup> )	NR	Abdominal pain	No/complete	NR	Positive/NR	NR
21/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/2 days	Generalized abdominal pain, diarrhea, abuse	Yes/improvement	NR/eating disorder	Positive/NR	Probable
79/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/1 day	Abdominal pain, diarrhea	Yes/improvement	NR	Positive/NR	Probable

Continues

**Supplementary Table 1b**  
Continued

Age (year)/gender	Components* (brand name)	Duration of use/latency <sup>a</sup>	Adverse events	Hospitalization/recovery	Other medications/concomitant conditions	Dechallenge/rechallenge	Causality assessment
70/M	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	5 days/4 days	Enteritis	Yes/complete	NR/chronic kidney failure, hypertension	Positive/NR	Possible
75/M	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	1 day/1 day	Diarrhea, asthenia, abuse	Yes/improvement	1. sodium picosulfate 2. macrogol (associations)	Positive/NR	Possible
72/F	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	NR	Hematochezia	Yes/NR	NR/anovulvar fistula, fasciitis, insulin-dependent diabetes mellitus, atrial fibrillation	NR	Possible
4/M	Senna leaf sennosides a and b (X Prep <sup>®</sup> )	1 day/1 day	Abdominal pain, asthenia, dehydration, diarrhea, abnormal complete blood count, vomiting	Yes/complete	NR/atopy	NR	Probable
32/F	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	1 day/1 day	Diarrhea, abdominal pain	Yes/improvement	NR	Yes Positive/NR	NR
76/F	Senna leaf sennosides a and b (X Prep <sup>®</sup> )	1 day/1 day	Ulcerative esophagitis, necrotizing esophagitis	Yes/NR	NR	NR	Probable
35/F	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	1 day/1 day	Abdominal cramps	Yes/complete	NR/cramped abdominal pain, acute diarrhea	NR	NR
25/F	Ispaghula (psyllium seeds) (Agiolax <sup>®</sup> )	1 day/1 day	Right hypochondrion pain, chest pain, abuse, stomach acidity	Yes/improvement	1. fluoxetine 2. carbamazepine 3. flurazepam/ pancreatitis, anorexia nervosa, cocaine abuse, bipolar disorder	NR	NR
NR/F	<i>Cassia angustifolia</i> , <i>Cassia fistula</i> (Tamarine <sup>®</sup> )	1 day/NR	Irregular bowel movements	NR/NR	NR/intestinal polyp-surgical removal	NR	Possible
67/M	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	1 day/1 day	Lipothymia	No/complete	1. macrogol 2. repaglinide 3. furosemide 4. codeine and paracetamol 5. amlodipine 6. enalapril 7. paroxetine 8. solifenacin 9. gabapentin/cerebral hemorrhage, intestinal resection, rectal hemorrhage, diabetes, hypertension	Positive/NR	NR
60/F	<i>Cassia angustifolia</i> , <i>Cassia fistula</i> (Tamarine <sup>®</sup> )	NR	Insomnia	No/NR	NR	NR	NR
86/F	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	1 day/2 days	Syncopal attack	Yes/NR	NR/cognitive deterioration, vulvectomy, vascular encephalopathy	NR	Possible
52/F	Senna leaf sennosides a and b (X Prep <sup>®</sup> )	1 day/1 day	Agitation, vomiting	Yes/improvement	NR/colonoscopy	Yes Positive/NR	Possible
15/M	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	1 day/1 day	Mental confusion, drowsiness	Yes/NR	1. azithromycin 2. paracetamol 3. almotriptan 4. levocetirizine 5. ramipril	Positive/NR	NR
76/F	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	1 day/1 day	Confusional state, dehydration, hyponatremia, vomiting	Yes/improvement	Enalapril	NR	Possible

Continues

### Supplementary Table 1b

Continued

Age (year)/gender	Components* (brand name)	Duration of use/latency <sup>b</sup>	Adverse events	Hospitalization/recovery	Other medications/concomitant conditions	Dechallenge/rechallenge	Causality assessment
86/M	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/1 day	Tonic-clonic convulsions, syncope	Yes/improvement	NR/neonatal encephalopathy	Positive/NR	NR
22/M	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/1 day	Syncope	Yes/complete	1. alprazolam 2. folic acid 3. estradiol	Positive/NR	Probable
73/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/1 day	Syncope, diarrhea, femur fracture	Yes/improvement	NR	Positive/NR	Possible
56/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/1 day	Speech alteration, abuse	Yes/complete	1. zopiclone	NR	Possible
90/M	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/1 day	Reduced movements, marked agitation, slowed thinking, increased blood creatine phosphokinase, dehydration, diarrhea, laxative abuse, hyperpyrexia, hypokalemia	Yes/improvement	NR/diabetes mellitus type 2, diabetic dyslipidemia, atrial fibrillation, stroke, benign prostatic hypertrophy, hypertension	Positive/NR	Possible
89/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	NR	Syncope, abdominal pain, diarrhea, vomiting	Yes/complete	NR	Positive/NR	Probable
74/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	3 days/1 day	Rash	No/complete	NR	Positive/NR	NR
64/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	4days/4 days	Rash	No/complete	1. domperidone 2. carbamazepine 3. pregabalin 4. clonazepam 5. interferon beta-1a 6. enalapril	Positive/NR	NR
81/M	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/1 day	Exanthem	No/improvement	NR/second degree atrioventricular block, heart failure, diabetes, gallbladder stones, cardiac pacemaker, dyslipidemia	Positive/NR	NR
55/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/1 day	Urticaria	No/improvement	NR	NR	NR
38/M	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	5 days/6 days	Urticaria	No/NR	NR	NR	NR
66/M	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/1 day	Rash	No/complete	NR/same reaction appeared with captopril	Positive/NR	NR
67/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/2 days	Urticaria	No/complete	NR	NR	Probable
70/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/1 day	Urticaria	No/complete	NR	NR	NR
81/F	Senna leaf sennosides a and b (X Prep <sup>†</sup> )	NR	Rash erythematous, dyspnoea	Yes/NR	NR	NR	NR
80/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	NR	Allergic urticaria	Yes/improvement	NR/thyroidectomy, renal cysts, coprostasis	NR	NR
55/F	Ispaghula (psyllium seeds) (Agiolax <sup>†</sup> )	1 day/1 day	Quincke's edema, urticaria	Yes/complete	1. amlodipine/hypertension	Positive/NR	NR
53/M	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	1 day/5 days	Erythematous rash	NR/NR	1. iohexol	NR	NR
90/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	4 months/30 days	Blood pressure variation, body temperature increase	No/complete	NR/rhinitis	Positive/positive	Possible
23/F	Senna leaf pure sennosides (Pursennid <sup>†</sup> )	NR	Hypotension, intestinal pain, nausea, dizziness	No/persistent	NR	NR	NR

Continues



**Supplementary Table 1b**  
Continued

Age (year)/gender	Components* (brand name)	Duration of use/latency <sup>b</sup>	Adverse events	Hospitalization/recovery	Other medications/concomitant conditions	Dechallenge/rechallenge	Causality assessment
NR/M	Herbal tea kelemata <sup>c</sup>	NR	Increase in INR, increase in prothrombin time	No/improvement	NR	Positive/NR	NR
88/M	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	1 day/2 days	Increase in INR	No/complete	1. warfarin 2. cardioaspirin 3. nebivolol 4. amlodipine 5. ranitidine 6. estazolam 7. furosemide	NR	NR
85/M	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	1 day/4 days	Decrease in INR	No/complete	1. warfarin 2. furosemide 3. losartan 4. amiodarone 5. simvastatin 6. bicatulamide 7. alendronate 8. repaglinide	Positive/NR	NR
72/F	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	8 days/12 days	Increase in INR	No/complete	1. warfarin 2. ibuprofen 3. paroxetine 4. haloperidol	Positive/NR	NR
81/M	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	20 days/24 days	Increase in INR	No/complete	1. warfarin 2. amiodarone 3. doxazosina 4. enalapril 5. furosemide 6. acetylsalicylic acid	NR	NR
70/F	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	1 day/7 days	Increase in INR	No/complete	1. warfarin 2. amiodarone 3. simvastatin 4. omega-3-triglycerides including other esters and acids 5. carvedilol 6. ramipril	Positive/NR	NR
72/M	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	2 days/2 days	Increase in INR	No/complete	1. warfarin 2. metoclopramide 3. amiodarone 4. acetylsalicylic acid 5. furosemide 6. canrenoate 7. valsartan 8. carvedilol 9. simvastatin	NR	NR
71/M	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	20 days/18 days	Decrease in INR	No/complete	1. warfarin 2. omeprazole 3. hydrochlorothiazide 4. potassium sparing 5. omega-3-triglycerides including other esters and acids	NR	NR
86/M	Senna leaf pure sennosides (Pursennid <sup>d</sup> )	1 day/1 day	Hypotension, soft stools	No/improvement	1. ramipril	Positive/NR	NR
88/M	<i>Cassia angustifolia</i> , <i>Cassia fistula</i> (Tamarine <sup>e</sup> )	5 days/40 days	Increase in INR	No/complete	1. warfarin 2. clopidogrel 3. acetylsalicylic acid 4. losartan 5. furosemide 6. glimepiride 7. rabeprazole 8. carvedilol	Positive/NR	NR

Continues

### Supplementary Table 1b

Continued

Age (year)/gender	Components <sup>a</sup> (brand name)	Duration of use/latency <sup>b</sup>	Adverse events	Hospitalization/recovery	Other medications/concomitant conditions	Dechallenge/rechallenge	Causality assessment
32/F	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	NR	Hypotension, watery diarrhoea, hypokalemia, voluntary overdose	Yes/NR	NR	NR	Probable
83/F	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	1 year/16 months	Hyponatremia	Yes/complete	1. meprazole 2. atenolol 3. other diuretics 4. pregabalin/hallucinations	Positive/NR	Probable
45/F	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	3 days/3 days	Asthenia, low potassium levels	Yes/complete	NR/anorexia nervosa, urinary tract infection, allergy to diclofenac	Positive/NR	Possible
70/M	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	20 days/19 days	Hyponatremia	Yes/complete	NR/idiopathic constipation	NR	Probable
90/M	Senna leaf, sennosides a and b (X Prep <sup>®</sup> )	NR	Hyponatremia	Yes/complete	1. clopidogrel 2. digoxin 3. levothyroxine 4. tamsulosin 5. levodopa 6. decarboxylase inhibitors/atrial fibrillation, vascular dementia, hypothyroidism	Positive/NR	Possible
87/F	Castor oil	1 day/1 day	Hyponatremia, dehydration	Yes/complete	1. neбиволol 2. betahistine 3. acetylsalicylic acid	Positive/NR	Probable
93/F	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	NR/3 years	Dark urine	No/NR	1. levodopa and decarboxylase inhibitors 2. bromazepam 3. lansoprazole 4. mirtazapine 5. paroxetine 6. quetiapine/Parkinson's disease, osteoarthritis, depression, gastritis, chronic constipation	NR	NR
NR/F	Ispaghula (psyllium seeds) (Agiolax <sup>®</sup> )	NR	Abuse	No/persistent	NR	NR	NR
73/M	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	5 days/30 days	Hematoma, pain, discromia	Yes/resolution with sequelae	1. warfarin 2. lactulose 3. paracetamol 4. tramadol/constipation, anticoagulant therapy	Positive/NR	NR
45/F	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	NR	Abuse, intentional self-harm	Yes/improvement	NR/depression, bipolar disorder	NR	NR
88/F	Senna leaf pure sennosides (Pursennid <sup>®</sup> )	5 days/5 days	Jaundice	No/improvement	lactitol (Portolac <sup>®</sup> )/exposed humerus fracture	Positive/NR	NR

F: Female; M: male; NR: not reported.

<sup>a</sup>As reported on product label.

<sup>b</sup>Latency = time from the beginning of treatment until the onset of the adverse event.