



# Summary of Investigation Results

## Preparations containing insulin

May 19, 2020

### **Non-proprietary name**

See Attachment

### **Branded name (Marketing authorization holder)**

See Attachment

### **Indications**

a.-l., o. Diabetes mellitus for which insulin therapy is indicated

m.-n. Type 2 diabetes mellitus for which insulin therapy is indicated

### **Summary of revisions**

The following should be added to the IMPORTANT PRECAUTIONS section.

Specific instructions to patients concerning changing injection sites to prevent cutaneous amyloidosis and lipodystrophy

Precaution for poor glycemic control and hypoglycemia secondary to administration into sites where cutaneous amyloidosis or lipodystrophy developed

### **Investigation results and background of the revision**

MHLW/PMDA in consultation with expert advisors concluded that revision of the package insert was necessary based on:

- Cases of cutaneous amyloidosis or lipodystrophy occurring following administration of preparations containing insulin and cases of poor glycemic control and of hypoglycemia both secondary to injection into the affected area have been reported in patients treated with preparations containing insulin in Japan.

*This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

• Several research papers have been identified that suggest a potential effect of cutaneous amyloidosis and lipodystrophy on glycemic control.

### **Number of cases and patient mortalities reported in Japan during the previous 3 fiscal years**

Cases involving cutaneous amyloidosis

a., g., j.

1 case each\* has been reported to date. No patient mortalities have been reported to date.

b.

A total of 7 cases\* have been reported to date. No patient mortalities have been reported to date.

(Japanese market launch: Humalog Injection MirioPen HD, July 2018; Lyumjev Injection 100 U/mL, Lyumjev Injection Cart, Lyumjev Injection MirioPen, Lyumjev Injection MirioPen HD; to be launched)

c., d., h., i., k. to o.

No cases have been reported to date.

(Japanese market launch: Xultophy combination Injection FlexTouch, September 2019; Soliqua Injection SoloStar, Insulin Lispro BS Injection HU 100 units/ml [Sanofi] Insulin Lispro BS Injection HU Cart [Sanofi], Insulin Lispro BS Injection HU SoloStar [Sanofi] to be launched)

e.

A total of 4 cases\* have been reported to date. No patient mortalities have been reported to date.

(Japanese market launch: Fiasp Injection 100 U/mL, Fiasp Injection FlexTouch, Fiasp Injection Penfill, February 2020)

f.

A total of 8 cases\* have been reported to date. No patient mortalities have been reported to date.

Cases involving lipodystrophy with secondary poor glycemic control

**Pharmaceuticals and Medical Devices Agency**



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a., e.

1 case\* each has been reported to date. No patient mortalities have been reported to date.  
(Japanese market launch: Fiasp Injection 100 U/mL, Fiasp Injection FlexTouch, Fiasp Injection Penfill, February 2020)

b. to d., g. to o.

No cases have been reported to date.

(Japanese market launch: Humalog Injection MirioPen HD, July 2018; Xultophy combination Injection FlexTouch, September 2019; Lyumjev Injection 100 U/mL, Lyumjev Injection Cart, Lyumjev Injection MirioPen, Lyumjev Injection MirioPen HD, Soliqua Injection SoloStar, Insulin Lispro BS Injection HU 100 units/ml [Sanofi], Insulin Lispro BS Injection HU Cart [Sanofi], Insulin Lispro BS Injection HU SoloStar [Sanofi] to be launched)

f.

A total of 2 cases\* have been reported to date. No patient mortalities have been reported to date.

\*The causal relationship between the drug and event was not evaluated.

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the "Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8, dated December 25, 2008).



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Attachment

Non-proprietary name	Brand name	Marketing authorization holder	
a. Insulin human (genetical recombination)	Novolin R 100 IU/mL, Novolin R FlexPen	Novo Nordisk Pharma Ltd.	
	Novolin 30R FlexPen, InnoLet 30R		
	Novolin N FlexPen		
	Humulin R Injection 100 units/mL, Humulin R Injection Cart, Humulin R Injection MirioPen	Eli Lilly Japan K.K.	
	Humulin 3/7 Injection 100 units/mL, Humulin 3/7 Injection Cart, Humulin 3/7 Injection MirioPen		
	Humulin N Injection 100 units/mL, Humulin N Injection Cart, Humulin N Injection MirioPen		
b. Insulin lispro (genetical recombination)	Humalog Injection 100 units/mL, Humalog Injection Cart, Humalog Injection MirioPen, Humalog Injection MirioPen HD	Eli Lilly Japan K.K.	
	Lyumjev Injection 100 U/mL, Lyumjev Injection Cart, Lyumjev Injection MirioPen, Lyumjev Injection MirioPen HD		
c. Insulin lispro mix preparation 25	Humalog Mix Injection 25 Cart, Humalog Mix Injection 25 MirioPen		
d. Insulin lispro mix preparation 50	Humalog Mix Injection 50 Cart, Humalog Mix Injection 50 MirioPen		
e. Insulin aspart (genetical recombination)	NovoRapid 30 Mix FlexPen, NovoRapid 30 Mix Penfill	Novo Nordisk Pharma Ltd.	
	NovoRapid 50 Mix FlexPen		
	NovoRapid 70 Mix FlexPen		
	NovoRapid 100 U/mL, NovoRapid FlexTouch, NovoRapid FlexPen, NovoRapid InnoLet, NovoRapid Penfill		
	Fiasp Injection 100 U/mL, Fiasp Injection		



Non-proprietary name	Brand name	Marketing authorization holder
	FlexTouch, Fiasp Injection Penfill	
f. Insulin glargine (genetical recombination)	Lantus XR inj. SoloStar Lantus Inj. 100 U/mL, Lantus Inj. Cart, Lantus Inj. SoloStar	Sanofi K.K.
g. Insulin detemir (genetical recombination)	Levemir FlexPen, Levemir InnoLet, Levemir Penfill	Novo Nordisk Pharma Ltd.
h. Insulin glulisine (genetical recombination)	Apidra Inj. 100 U/mL, Apidra Inj. Cart, Apidra Inj. SoloStar	Sanofi K.K.
i. Insulin degludec (genetical recombination)	Tresiba FlexTouch, Tresiba Penfill	Novo Nordisk Pharma Ltd.
j. Insulin glargine (genetical recombination) [insulin glargine biosimilar 1]	Insulin Glargine BS Inj. Cart [Lilly], Insulin Glargine BS Inj. MirioPen [Lilly]	Eli Lilly Japan K.K.
k. Insulin glargine (genetical recombination) [insulin glargine biosimilar 2]	Insulin Glargine BS Injection Kit [FFP]	FUJIFILM Toyama Chemical Co., Ltd.
l. Insulin degludec (genetical recombination)/ insulin aspart (genetical	Ryzodeg FlexTouch	Novo Nordisk Pharma Ltd.

Non-proprietary name	Brand name	Marketing authorization holder
recombination)		
m. Insulin degludec (genetical recombination)/ liraglutide (genetical recombination)	Xultophy combination Injection FlexTouch	Novo Nordisk Pharma Ltd.
n. Insulin glargine (genetical recombination)/ lixisenatide	Soliqua Injection SoloStar	Sanofi K.K.
o. Insulin lispro (genetical recombination) [insulin lispro biosimilar 1]	Insulin Lispro BS Injection HU 100 units/ml [Sanofi] Insulin Lispro BS Injection HU Cart [Sanofi], Insulin Lispro BS Injection HU SoloStar [Sanofi]	Sanofi K.K.