Review Report

June 27, 2016

Pharmaceuticals and Medical Devices Agency

The following are the results of a review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

Brand Name	Inavir Dry Powder Inhaler 20 mg
Non-proprietary Name	Laninamivir Octanoate Hydrate (JAN*)
Applicant	Daiichi Sankyo Company, Limited
Date of Application	October 7, 2015
Dosage Form/Strength	Dry powder for inhalation: One inhaler contains 20.76 mg of Laninamivir Octanoate Hydrate (equivalent to 20 mg of laninamivir octanoate).
Application Classification	Prescription drug, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product, when administered at the proposed dosages and administration, in preventing influenza A or B virus infection, and acceptable safety in view of the benefits indicated by the data submitted, as shown in Attachment.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below.

Indication

Treatment and prophylaxis of influenza A or B virus infection

(No change)

Dosage and Administration

1. Therapeutic use

Adults:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose.

Children aged <10 years:

Laninamivir octanoate 20 mg is administered by inhalation as a single dose.

Children aged ≥10 years:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose.

2. Prophylactic use

Adults:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose. Alternatively, laninamivir octanoate 20 mg may be administered by inhalation once daily for 2 days.

Children aged <10 years:

Laninamivir octanoate 20 mg is administered by inhalation as a single dose.

Children aged ≥10 years:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose. Alternatively, laninamivir octanoate 20 mg may be administered by inhalation once daily for 2 days.

(Underlines denote addition.)

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

April 20, 2016

The following is an outline of the data submitted by the applicant and content of the review by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Inavir Dry Powder Inhaler 20 mg
Non-proprietary Name	Laninamivir Octanoate Hydrate
Applicant	Daiichi Sankyo Company, Limited
Date of Application	October 7, 2015
Dosage Form/Strength	Dry powder for inhalation: One inhaler contains 20.76 mg of Laninamivir Octanoate Hydrate (equivalent to 20 mg of laninamivir octanoate).
Proposed Indication	Treatment and prophylaxis of influenza A or B virus infection

Proposed Dosage and Administration

1. Therapeutic use

Adults:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose.

Children aged <10 years:

Laninamivir octanoate 20 mg is administered by inhalation as a single dose.

Children aged ≥10 years:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose.

2. Prophylactic use

Adults:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose. Alternatively, laninamivir octanoate 20 mg may be administered by inhalation once daily for 2 days.

Children aged <10 years:

Laninamivir octanoate 20 mg is administered by inhalation as a single dose.

Children aged ≥10 years:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose. Alternatively, laninamivir octanoate 20 mg may be administered by inhalation once daily for 2 days.

(Note: Partial change application filed for approval of new additional dosage and administration for prophylactic use in adults and children)

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List of Abbreviations

FAS	Full analysis set
PCR	Polymerase Chain Reaction
PMDA	Pharmaceuticals and Medical Devices Agency
Inavir	Inavir Dry Powder Inhaler 20 mg
Laninamivir octanoate	Laninamivir Octanoate Hydrate

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Laninamivir Octanoate Hydrate (hereinafter referred to as laninamivir octanoate) is an influenza antiviral drug discovered by Daiichi Sankyo Company, Limited. Laninamivir octanoate is metabolized to its active metabolite R-125489, which suppresses the replication of influenza A and B viruses by selectively inhibiting neuraminidase present on the surface of these viruses. In Japan, the product containing laninamivir octanoate as the active ingredient (brand name, Inavir Dry Powder Inhaler 20 mg [hereinafter referred to as Inavir]) was approved in September 2010 for the indication of "treatment of influenza A or B virus infection." In December 2013, the indication and dosage and administration were expanded to include those for prophylactic use.

In the review of clinical study data submitted in the previous application for the new indication and dosage and administration for prophylactic use, PMDA accepted "laninamivir octanoate 20 mg administered by inhalation once daily for 2 days." Meanwhile, PMDA instructed the applicant to develop a single-dose prophylactic regimen of the product for dosing convenience, in expectation of a prophylactic effect of the approved therapeutic regimen, "laninamivir octanoate 40 mg administered by inhalation as a single dose." PMDA further instructed the applicant to develop the prophylactic dosage regimen for children aged <10 years, despite the difficulty to determine a dosage regimen for children in this age group. It is a fact that children aged <10 years also constitute a population at high risk for influenza virus infection, and this warrants the use of the product for the prophylaxis of influenza in this population.

In response, the applicant conducted 2 clinical studies (a single dose study in subjects aged ≥10 years and a prophylaxis study in children aged <10 years). Based on the results of these studies, the applicant submitted a partial change application for new dosage and administration for prophylactic use in children and adults.

Inavir has not been approved overseas as of March 2016.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

No new study data were submitted with the present application.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

No new study data were submitted with the present application.

4. Non-clinical Pharmacokinetic and Outline of the Review Conducted by PMDA

No new study data were submitted with the present application.

5. Toxicology and Outline of the Review Conducted by PMDA

No new study data were submitted with the present application.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

No new study data were submitted with the present application.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The efficacy and safety data submitted consisted of the results of a phase III study in children aged <10 years and a phase III study in subjects aged ≥10 years. Table 1 summarizes these studies. The dose of Inavir is expressed as the amount of laninamivir octanoate.

Table 1. Summary of efficacy and safety results in clinical studies

Study (phase)	Subjects	Study design	Dosage regimen (FAS)
CS8958-A-J308 (III)	Children aged <10 years	Randomized, double-blind, placebo-controlled, parallel group study	• Laninamivir octanoate 20 mg single dose inhalation (N = 171) • Placebo single dose inhalation (N = 170)
CS8958-A-J309 (III)	Subjects aged ≥10 years	Randomized, double-blind, placebo-controlled, parallel group study	• Laninamivir octanoate 40 mg single dose inhalation (N = 267) • Laninamivir octanoate 20 mg once daily inhalation for 2 days (N = 269) • Placebo once daily inhalation for 2 days (N = 265)

7.1 Japanese phase III studies

7.1.1 Prophylaxis study in children (CTD 5.3.5.1-1, Study CS8958-A-J308 [November 2014 to March 2015])

A randomized, double-blind, placebo-controlled, parallel group study was conducted at 50 centers in Japan. The study aimed to evaluate the efficacy and safety of inhaled laninamivir octanoate 20 mg administered as a single prophylactic dose to children aged <10 years[1)] who were family or household contacts of an index patient[2)] with influenza A or B virus infection (target sample size, 300 subjects).

Subjects received a single dose of inhaled laninamivir octanoate 20 mg or placebo.

Of 343 randomized subjects (172 in the laninamivir octanoate group and 171 in the placebo group), 341 subjects (171 in the laninamivir octanoate group and 170 in the placebo group) received the study drug. All of the treated subjects were included in the full analysis set (FAS) and the safety analysis population. The FAS was used for the efficacy analysis.

The incidence of laboratory-confirmed influenza virus infection was the primary endpoint of the study. It was defined as the percentage of subjects who (a) had a positive polymerase chain reaction (PCR) result, (b) had a body temperature of ≥37.5°C, and (c) experienced ≥2 of the predefined influenza symptoms (headache, myalgia or arthralgia, fatigue, chills or sweating, nasal symptoms, sore throat, and cough) during the observation period (from the day of study drug administration [Day 1] through Day 11). Results are shown in Table 2. A pairwise comparison showed a statistically significant difference between placebo and laninamivir octanoate, demonstrating the superiority of a single dose of laninamivir octanoate 20 mg to placebo.

Table 2. Incidence of laboratory-confirmed influenza virus infection (FAS)

Treatment group	N	Number of infected subjects (%)	*P* value[a)]	Relative risk reduction (%) (95% confident interval [CI])
Laninamivir octanoate	171	18 (10.5)	0.0232	45.8 (7.5, 68.2)
Placebo	170	33 (19.4)		

a) Fisher's exact test

Adverse events (including abnormal laboratory changes) were observed in 14.6% (25 of 171) of subjects in the laninamivir octanoate group and in 12.9% (22 of 170) of subjects in the placebo group. Of these, adverse events considered by the investigator (or subinvestigator) to be causally related to the study drug (adverse drug reactions) were 1.2% (2 subjects) in the laninamivir octanoate group and 0.6% (1 subject) in the placebo group. Adverse events occurring in ≥1% of subjects in any group were nasopharyngitis (4.1% [7 subjects] in the laninamivir octanoate group, 1.2% [2 subjects] in the placebo group), upper respiratory tract inflammation (2.9% [5 subjects], 3.5% [6 subjects]), pharyngitis (1.2% [2 subjects], 1.2% [2 subjects]), bronchitis (0.6% [1 subject], 1.2% [2 subjects]), gastroenteritis (0.6% [1 subject], 1.8% [3 subjects]), blood urine present (none [0 subjects] vs. 1.2% [2 subjects]), and protein urine present (0 subjects, 1.2% [2 subjects]). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

1) Subjects who were assessed by the investigator (or subinvestigator) at informed consent not to have influenza virus infection and to be capable of inhaling the drug using the dedicated inhaler

2) Patients who tested positive with the influenza virus test kit and were the first to be infected with influenza A or B virus in the 2014/2015 season among their family or household members

7.1.2 Single-dose prophylaxis study (CTD 5.3.5.1-2, Study CS8958-A-J309 [November 2014 to March 2015])

A randomized, double-blind, placebo-controlled, parallel group study was conducted at 50 centers in Japan. The study aimed to evaluate the efficacy and safety of inhaled laninamivir octanoate 40 mg administered as a single prophylactic dose to subjects aged ≥10 years[3)] who were family or household contacts of an index patient[1)] with influenza A or B virus infection (target sample size, 750 subjects).

Subjects allocated in the 40 mg single-dose group received laninamivir octanoate 40 mg once on Day 1 and placebo once on Day 2 by inhalation. Subjects allocated in the 20 mg 2-dose group received laninamivir octanoate 20 mg and placebo once on Day 1 and laninamivir octanoate 20 mg once on Day 2 by inhalation. Subjects allocated in the placebo group received placebo by inhalation once daily on Days 1 and 2.

Of 803 randomized subjects (267 in the 40 mg single-dose group, 269 in the 20 mg 2-dose group, and 267 in the placebo group), 801 subjects received the study drug (267 in the laninamivir octanoate 40 mg single-dose group, 269 in the laninamivir octanoate 20 mg × 2 group, 265 in the placebo group). All the treated subjects were included in the FAS and in the safety analysis population. The FAS was used for the efficacy analysis.

The primary endpoint of the study was the incidence of laboratory-confirmed influenza virus infection [see "7.1.1 Prophylactic study in children" for the definition]. The results are shown in Table 3. A pairwise comparison showed a statistically significant difference between the placebo group and the 40 mg single-dose group, demonstrating the superiority of a single dose of laninamivir octanoate 40 mg to placebo.

Table 3. Incidence of laboratory-confirmed influenza virus infection (FAS)

Treatment group	N	No. of infected subjects (%)	*P* value [a)]	Relative risk reduction rate (%) [95% CI]
Laninamivir octanoate 40 mg single-dose	267	12 (4.5)	0.0015	62.8 [29.3, 80.4]
Laninamivir octanoate 20 mg 2-dose	269	12 (4.5)		63.1 [29.8, 80.5]
Placebo	265	32 (12.1)		

[a)] Fisher's exact test (pairwise comparison with the placebo group)

Adverse events (including abnormal laboratory changes) were observed in 11.6% (31 of 267) of subjects in the 40 mg single-dose group, in 11.2% (30 of 269) of subjects in the 20 mg 2-dose group, and in 12.1% (32 of 265) of subjects in the placebo group. Of these, adverse drug reactions were 1.9% (5 of 267 of subjects) in the 40 mg single-dose group, 1.9% (5 of 269of subjects) in the 20 mg 2-dose group, and 1.5% (4 of 265) of subjects in the placebo group. Adverse events occurring in ≥1% of subjects in any group were nasopharyngitis (3.4% [9 subjects] in the 40 mg single-dose group, 3.0% [8 subjects] in the 20 mg 2-dose group, 4.2% [11subjects] in the placebo group), glucose urine present (1.5% [4 subjects], 0.4% [1 subject], 0.4% [1subject]), upper respiratory tract inflammation (1.1% [3 subjects], 1.5% [4 subjects], 1.1% [3 subjects]), headache (1.1% [3 subjects], 0.7% [2 subjects], 0.4% [1 subject]), and pharyngitis (0 subjects, 1.5% [4subjects], 1.1% [3 subjects]).

There were no deaths or serious adverse events.

An adverse event leading to treatment discontinuation (migraine) occurred in 1 subject in the placebo group.

7.R Outline of the review conducted by PMDA

7.R.1 Development history and efficacy of laninamivir octanoate

In the review of the previous application for the new dosage and administration for prophylaxis of influenza (see Review Report of Inavir Dry Powder Inhaler 20 mg, [November 5, 2013]), PMDA instructed the applicant to develop a single-dose prophylactic regimen of the product for dosing

[3)] Subjects aged ≥10 years who were assessed not to have influenza virus infection by the investigator (or subinvestigator) at informed consent

convenience, in expectation of the efficacy of a single dose of inhaled laninamivir octanoate in the prophylaxis of influenza virus infection, based on the following findings:

- A clinical pharmacology study was conducted to investigate the pharmacokinetics of laninamivir octanoate in the target tissue. After a single dose of inhaled laninamivir octanoate 40 mg, the concentrations of R-125489 in alveolar mucus and alveolar macrophages remained higher than the 50% inhibitory concentration (IC_{50}) against neuraminidases of influenza A and B viruses for an extended period.

- The Japanese phase III study (Study CS8958-A-J306 [Study J306]) was conducted to investigate the prophylactic effect of inhaled laninamivir octanoate 20 or 40 mg once weekly (a total of 2 doses). The occurrence of laboratory-confirmed influenza virus infection tended to be prevented.

- The efficacy of a single dose of inhaled laninamivir octanoate 40 mg was confirmed in the treatment of influenza virus infection.

In the review of the previous application (see Review Report of Inavir Dry Powder Inhaler 20 mg [November 5, 2013]), because of the need of the product for use in children aged <10 years, PMDA also instructed the applicant to develop a prophylactic regimen for this population.

In response to PMDA's instructions, the applicant conducted a single-dose prophylaxis study in subjects aged ≥10 years (Study CS8958-A-J309 [Study J309]) and a prophylaxis study in children aged <10 years (Study CS8958-A-J308 [Study J308]) and submitted the results of these studies as data that support the efficacy and safety of laninamivir octanoate in the prophylaxis of influenza.

In Study J309, subjects received a single dose of inhaled laninamivir octanoate 40 mg and inhaled laninamivir octanoate 20 mg once daily for 2 days. The dosage regimens were determined based on the above-mentioned observations.

A single dose of inhaled laninamivir octanoate 20 mg was selected as the dosage regimen for Study J308. The applicant selected this dosage regimen, considering that the prophylactic dose would not need to be higher than the dose used for the treatment of influenza virus infection in children aged <10 years (a single dose of inhaled laninamivir octanoate 20 mg).

PMDA evaluated the efficacy of laninamivir octanoate in the prophylaxis of influenza A or B virus infection, based on the results of pivotal Studies J308 and J309. The studies demonstrated the promising efficacy of a single dose of inhaled laninamivir octanoate 40 mg in adults and children aged ≥10 years and of a single dose of inhaled laninamivir octanoate 20 mg in children aged <10 years.

7.R.1.1 Efficacy of laninamivir octanoate in adults and children aged ≥10 years

The applicant's explanation:

In Study J309 conducted in subjects aged ≥10 years, the incidence of laboratory-confirmed influenza virus infection (the primary endpoint) was 4.5% (12 of 267 of subjects) in the 40 mg single-dose group, 4.5% (12 of 269 of subjects) in the 20 mg 2-dose group, and 12.1% (32 of 265 of subjects) in the placebo group. A pairwise comparison showed a statistically significant difference between the placebo group and the 40 mg single-dose group ($P = 0.0015$, Fisher's exact test), demonstrating the superiority of a single dose of laninamivir octanoate 40 mg to placebo. The efficacy of 2 doses of laninamivir octanoate 20 mg, the approved dosage regimen, was comparable to that of a single dose of laninamivir octanoate 40 mg. Figure 1 shows time-course changes in the cumulative incidence of laboratory-confirmed influenza virus infection.

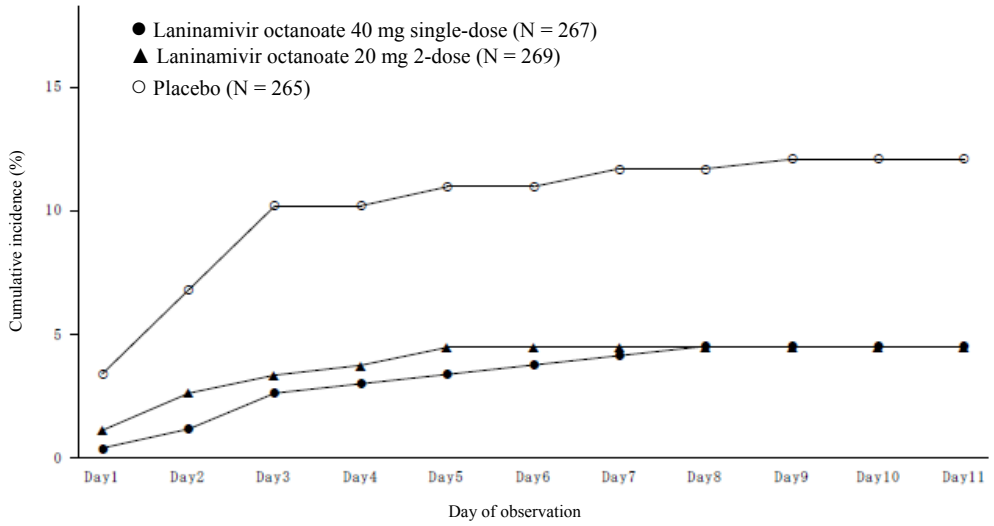

Figure 1. Time-course changes in the cumulative incidence of laboratory-confirmed influenza virus infection (FAS)

Table 8 shows the efficacy of laninamivir octanoate by age group. In the age group of 20 to 29 years, laboratory-confirmed influenza virus infection occurred more frequently in the laninamivir octanoate groups than in the placebo group. An analysis of causative factors revealed differences in some baseline characteristics of the subjects (sex, relation with the index patient, viral PCR test at enrollment [negative vs. positive], smoking) between the age group of 20 to 29 years and other groups, but failed to show any clear effect of these factors on laboratory-confirmed influenza virus infection. The higher incidence in the age group of 20 to 29 years was possibly due to the small number of subjects in this age group.

Table 8. Incidence of laboratory-confirmed influenza virus infection by age group in Study J309 (FAS)

	Treatment group	N	Number of infected patients (%)	Relative risk reduction (%) [95% CI]
All subjects	Laninamivir octanoate 40 mg single-dose	267	12 (4.5)	62.8 [29.3, 80.4]
	Laninamivir octanoate 20 mg 2-dose	269	12 (4.5)	63.1 [29.8, 80.5]
	Placebo	265	32 (12.1)	
10-19 years	Laninamivir octanoate 40 mg single-dose	35	1 (2.9)	52.9 [−396, 95.5]
	Laninamivir octanoate 20 mg 2-dose	40	1 (2.5)	58.8 [−335, 96.1]
	Placebo	33	2 (6.1)	
20-29 years	Laninamivir octanoate 40 mg single-dose	14	3 (21.4)	−286 [−3220, 55.2]
	Laninamivir octanoate 20 mg 2-dose	10	1 (10.0)	−80.0 [−2478, 87.4]
	Placebo	18	1 (5.6)	
30-39 years	Laninamivir octanoate 40 mg single-dose	101	2 (2.0)	88.3 [51.2, 97.2]
	Laninamivir octanoate 20 mg 2-dose	124	9 (7.3)	57.2 [9.8, 79.7]
	Placebo	118	20 (16.9)	
≥40 years	Laninamivir octanoate 40 mg single-dose	117	6 (5.1)	45.3 [−48.3, 79.8]
	Laninamivir octanoate 20 mg 2-dose	95	1 (1.1)	88.8 [13.1, 98.5]
	Placebo	96	9 (9.4)	

In the prophylaxis study conducted in the 2011/2012 season in subjects aged ≥10 years (Study CS8958-A-J307 [Study J307]), the efficacy and safety of inhaled laninamivir octanoate 40 mg as a single dose of were not assessed. However, the efficacy of the 2 doses of laninamivir octanoate 20 mg was not affected by age (see "4.(iii).B.(4) Dosage and administration" in Review Report [1] of the Review Report of Inavir Dry Powder Inhaler 20 mg [November 5, 2013]).

Thus, the reason remains unclear for more frequent laboratory-confirmed influenza virus infection in the laninamivir octanoate groups than in the placebo group among subjects aged 20 to 29 years in Study J309. Possibly it was an accidental result due to the small number of subjects in this age group. In Study

J307, age did not affect the efficacy. Thus, these studies failed to reach a conclusion that denies the efficacy of laninamivir octanoate in patients aged 20 to 29 years.

PMDA asked the applicant to explain the prophylactic effect of a single dose of inhaled laninamivir octanoate by type/subtype of influenza virus.

The applicant's explanation:
In both Studies J308 and J309, influenza A virus subtype H3N2 was detected in most index patients. The virus strains found in other index patients were influenza A (H1N1) pdm09 (3 patients) and influenza B (9 patients) in the 2 studies combined. None of the family or household contacts of the index patients infected with influenza A(H1N1) pdm09 or B virus experienced influenza virus infection.

In the prophylaxis study conducted in the 2009/2010 season (Study J306), the efficacy and safety of a single dose of inhaled laninamivir octanoate 40 mg were not evaluated. However, the incidence of laboratory-confirmed infection with influenza A (H1N1) pdm09 virus tended to be lower in the laninamivir octanoate groups than in the placebo group. In Study J307, the relative risk reduction for influenza B virus infection was lower than that for influenza A (subtype H3) virus infection. Also, influenza B virus tended to be less susceptible to laninamivir octanoate than influenza A virus, in light of the susceptibility of clinical isolates to laninamivir octanoate. However, the results of Study J307 showed that the efficacy of laninamivir octanoate in the prophylaxis of laboratory-confirmed influenza B virus infection was similar to that in the prophylaxis of influenza A (H3) virus infection, despite a limited number of subjects with influenza B virus infection. Laninamivir octanoate is therefore expected to have a certain efficacy in the prophylaxis of influenza B virus as well (see "4.(iii).B.(1) Efficacy" in Review Report [1] of the Review Report of Inavir Dry Powder Inhaler 20 mg [November 5, 2013]).

Thus, a single dose of inhaled laninamivir octanoate has a certain efficacy in the prophylaxis of both influenza A and B viruses. This conclusion is based on the following observations: (a) Data from Studies J308 and J309 revealed no cases of laboratory-confirmed influenza virus infection in subjects who were household contacts of index patients infected with influenza A (H1N1) pdm09 or B virus, although a majority of index patients had influenza A (H3N2) virus infection and a small minority had influenza A (H1N1) pdm09 or B virus infection in in both studies; (b) data from Studies J306 and J307 suggested a certain efficacy of laninamivir octanoate in the prophylaxis of infection with influenza A (H1N1) pdm09 and B viruses; and (c) according to the surveillance of drug-resistant strains among clinical isolates conducted by the National Institute of Infectious Diseases, no emergence of viruses resistant to laninamivir octanoate has been reported as of December 2015 (http://www.nih.go.jp/niid/ja/influ-resist.html [accessed in April 2016]).

PMDA's view on the efficacy of laninamivir octanoate:
Among the patients of the age group 20 to 29 years, laboratory-confirmed influenza virus infection tended to occur more frequently in the 40 mg single-dose group than in the placebo group, although the causative factor of this result is unclear. In Study J307, however, the incidence of laboratory-confirmed influenza virus infection among the age group 20 to 29 years tended to be lower in the 20 mg 2-dose group than in the placebo group. These observations indicate that age is unlikely to have a clinically significant impact on the efficacy of laninamivir octanoate.

Studies J308 and J309 provide only limited observations on the efficacy of laninamivir octanoate in the prophylaxis of infection with influenza virus strains other than influenza A (H3N2) virus. In addition, investigations of the susceptibility of clinical isolates show that influenza B virus tends to be less susceptible to laninamivir octanoate as compared with influenza A virus. However, a single dose of inhaled laninamivir octanoate has a certain efficacy in the prophylaxis of infection with both influenza A and B viruses, because of the following observations:

- Results of Studies J306 and J307 suggest that laninamivir octanoate has a certain efficacy in the prophylaxis of influenza A (H1N1) pdm09 and B viruses (see "II.4.(iii).B.(1) Efficacy" in Review Report [1] of the Review Report of Inavir Dry Powder Inhaler 20 mg [November 5, 2013]).
- As of December 2015, there has been no report of the emergence of laninamivir octanoate-resistant virus strains.

The results of Study J309 demonstrated the superiority of a single dose of laninamivir octanoate 40 mg to placebo in the prophylaxis of influenza. Taking account of this observation and the discussion thus far, PMDA concluded that the efficacy of a single dose of inhaled laninamivir octanoate 40 mg has been demonstrated in the prophylaxis of influenza virus infection in adults and children aged ≥10 years.

However, given circulating influenza virus strains varying from season to season, data supporting the efficacy of laninamivir octanoate in the prophylaxis of influenza virus infection should be further collected by type/subtype of the causative influenza virus detected in index patients, and new information should be promptly provided to healthcare professionals if it becomes available.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.1.2 Efficacy of laninamivir octanoate in children aged <10 years

The applicant's explanation:

In Study J308 in children aged <10 years, the incidence of laboratory-confirmed influenza virus infection (the primary endpoint) was 10.5% (18 of 171 of subjects) in the laninamivir octanoate group and 19.4% (33 of 170 of subjects) in the placebo group. A pairwise comparison revealed a statistically significant difference between placebo and laninamivir octanoate (P = 0.0232, Fisher's exact test), demonstrating the superiority of a single dose of inhaled laninamivir octanoate 20 mg to placebo. Figure 2 shows time-course changes in the cumulative incidence of laboratory-confirmed influenza virus infection. These results demonstrate the efficacy of a single dose of inhaled laninamivir octanoate 20 mg in the prophylaxis of influenza virus infection in children <10 years.

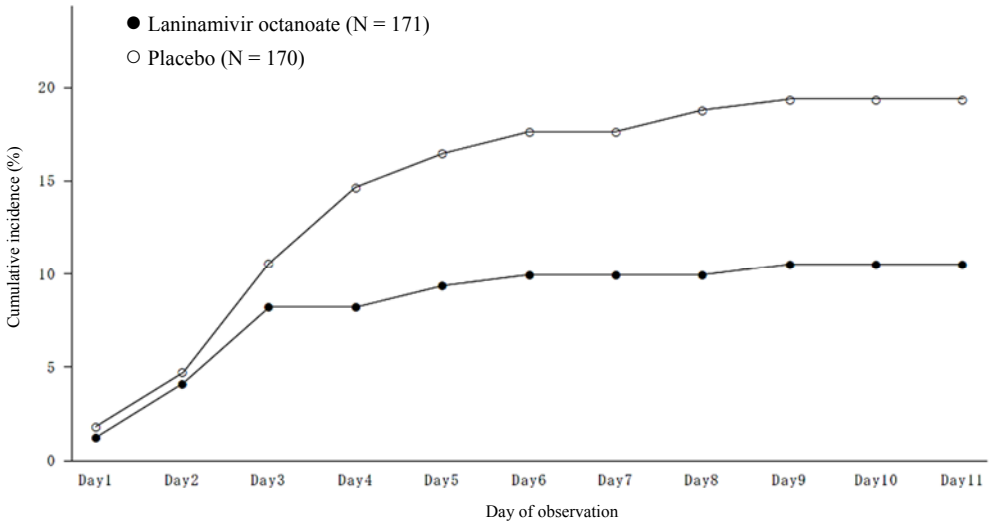

Figure 2. Time-course changes in cumulative incidence of laboratory-confirmed influenza virus infection (FAS)

PMDA's conclusion:

The superiority of a single dose of laninamivir octanoate 20 mg to placebo was demonstrated in Study J308 in children aged <10 years, and the result indicated the efficacy of a single dose of inhaled laninamivir octanoate 20 mg in the prophylaxis of influenza virus infection in children aged <10 years. Nevertheless, data should be further collected on the efficacy of laninamivir octanoate in the prophylaxis of influenza virus infection in children of this age group by type/subtype of influenza virus detected in each index patient, in a similar way it was done for adults and children aged ≥10 years. New information should be promptly communicated to healthcare professionals if it becomes available.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.2 Safety

7.R.2.1 Safety of laninamivir octanoate in Studies J308 and J309

Table 14 shows adverse events occurring in ≥1% of subjects in any laninamivir octanoate group in Studies J308 and J309. There were no adverse events classified as abnormal behavior/speech.[4)] There were no deaths, other serious adverse events, or adverse events leading to treatment discontinuation in any laninamivir octanoate group of either study.

Table 14. Adverse events occurring in ≥1% of subjects in any laninamivir octanoate group (Studies J308 and J309)

Event	Study J308		Study J309		
	Laninamivir octanoate 20 mg single-dose	Placebo	Laninamivir octanoate 40 mg single-dose	Laninamivir octanoate 20 mg 2-dose	Placebo
N	171	170	267	269	265
Any adverse event	25 (14.6)	22 (12.9)	31 (11.6)	30 (11.2)	32 (12.1)
Nasopharyngitis	7 (4.1)	2 (1.2)	9 (3.4)	8 (3.0)	11 (4.2)
Pharyngitis	2 (1.2)	2 (1.2)	0	4 (1.5)	3 (1.1)
Headache	0	0	3 (1.1)	2 (0.7)	1 (0.4)
Upper respiratory tract inflammation	5 (2.9)	6 (3.5)	3 (1.1)	4 (1.5)	3 (1.1)
Glucose urine present	0	0	4 (1.5)	1 (0.4)	1 (0.4)

N (%)

PMDA's view on the safety of laninamivir octanoate:
Studies J308 and J309 revealed no significant difference in the types or incidences of adverse events between laninamivir octanoate and placebo or in the safety between children and adults. The proposed dosage and administration for the present application is the same as that approved for the treatment of influenza virus infection, and the safety profile of laninamivir octanoate in the clinical studies was similar to the known one. Based on the above, there is no particular concern about the safety of laninamivir octanoate with the proposed dosage and administration.

No abnormal behavior or other related adverse events were observed in any clinical studies investigating the efficacy of laninamivir octanoate in the prophylaxis of influenza virus infection, including Studies J308 and J309. However, there are several studies reporting that psychoneurotic symptoms such as abnormal behavior occurred in children treated with an influenza antiviral drug, and the post-marketing surveillance on the use of laninamivir octanoate for the treatment of influenza virus infection revealed that abnormal behavior was experienced by patients treated with laninamivir octanoate (see "4.(iii).B.(2) Safety in Review Report [1] of the Review Report of Inavir Dry Powder Inhaler 20 mg [November 5, 2013]). Therefore, abnormal behavior and related events occurring in children and adolescents should be further monitored, and new information should be appropriately communicated to healthcare professionals if it becomes available.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.3 Use of laninamivir octanoate in high-risk populations

The applicant provided the following explanation on the efficacy and safety of laninamivir octanoate in the prophylaxis of influenza virus infection in high-risk populations (patients with decreased immune function, metabolic disease, chronic respiratory illness, chronic renal impairment, or chronic heart disease, and the elderly aged ≥65 years), because prophylactic laninamivir octanoate is expected to be used in these populations:
In Study J308, 4 subjects in the 20 mg single-dose group and 9 subjects in the placebo group belonged to any of the high-risk populations. Of these, none in the 20 mg single-dose group and 2 subjects in the placebo group experienced laboratory-confirmed influenza virus infection.

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4) Whether the patient had abnormal behavior/speech was determined by the investigator (or subinvestigator) based on the comparison with normal daily behavior according to the following criteria:
A: Abnormal behavior that may lead to an accident or harm other people
B: Hallucination visual, hallucination, confused sense
C: Taking in delirium, singing, meaningless movement
D: Scare, fear, getting angry, crying, laughing, lack of facial expression, unresponsiveness
E: Putting anything into his/her mouth

In Study J309, 7 subjects in the 40 mg single-dose group, 3 subjects in the 20 mg 2-dose group, and 10 subjects in the placebo group belonged to any of the high-risk populations. No laboratory-confirmed influenza virus infection occurred in any groups.

The safety analysis was performed for the high-risk subjects treated with laninamivir octanoate in Studies J308 and J309. Mild nasopharyngitis was the only adverse event that occurred in 1 subject in the 40 mg single-dose group of Study J309. There were no adverse events that may cause safety concerns.

In the 2 studies, there were no particular efficacy or safety concerns in the high-risk subjects, although only a small number of high-risk subjects received a single dose of inhaled laninamivir octanoate. There was no concern specific to the high-risk populations in the past clinical studies (Studies J306 and J307), albeit a different dosage regimen used (see "4.(iii).B.(3).1) High-risk population" in Review Report [1] of the Review Report of Inavir Dry Powder Inhaler 20 mg [November 5, 2013]). Also, the efficacy and safety in the high-risk populations showed no tendency to differ by dosage regimen.

Currently, a specified use-results survey is ongoing to gather data from the elderly aged ≥65 years receiving inhaled laninamivir octanoate 20 mg once daily for 2 days for the prophylaxis of influenza virus infection (the approved dosage regimen). As of September 9, 2015, a total of 48 elderly individuals were evaluated for the safety and efficacy of laninamivir octanoate. Neither adverse events nor adverse drug reactions occurred in the elderly individuals surveyed, nor did any of them experience influenza virus infection.[5)]

Based on the above, the applicant considers that single-dose inhaled laninamivir octanoate is expected to be effective in the high-risk populations and that there are no particular safety concerns.

PMDA's view:
There are only limited data on the efficacy and safety of single-dose inhaled laninamivir octanoate in the high-risk populations. However, taking account of the results of clinical studies conducted on the prophylaxis of influenza virus infection, the applicant's explanation (single-dose inhaled laninamivir octanoate is expected to be effective in the high-risk populations and there are no particular safety concerns) is acceptable.

7.R.4 Dosage and administration

Based on the discussions in Sections 7.R.1, 7.R.2, and 7.R.3 as well as on the review presented below, PMDA concluded that the following dosage and administration for the prophylaxis of influenza virus infection should be appropriate.

Adults:
Laninamivir octanoate 40 mg is administered by inhalation as a single dose. Alternatively, laninamivir octanoate 20 mg may be administered by inhalation once daily for 2 days.

Children aged <10 years:
Laninamivir octanoate 20 mg is administered by inhalation as a single dose.

Children aged ≥10 years:
Laninamivir octanoate 40 mg is administered by inhalation as a single dose. Alternatively, laninamivir octanoate 20 mg may be administered by inhalation once daily for 2 days.

(The underlined parts denote additions.)

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.4.1 Choice between single-dose and 2-dose regimens in adults and children aged ≥10 years

There are 2 options for dosage regimens for adults and children aged ≥10 years: single-dose inhalation of laninamivir octanoate 40 mg or 2-dose inhalation of laninamivir octanoate 20 mg. PMDA asked the applicant to explain how healthcare professionals should select the right dose in clinical use.

The applicant's explanation:

5) Had a positive viral PCR test result and a body temperature of ≥37.5°C or ≥1 of the following 7 influenza symptoms: headache, myalgia or arthralgia, fatigue, chills or sweating, nasal symptoms, sore throat, and cough.

The incidence of laboratory-confirmed influenza virus infection in Study J309 was 4.5% (12 of 267of subjects) in the 40 mg single-dose group, 4.5% (12 of 269 of subjects) in the 20 mg 2-dose group, and 12.1% (32 of 265 of subjects) in the placebo group, showing comparable efficacy between the 2 dosage regimens of laninamivir octanoate. The safety analysis also revealed no clear difference between the 2 dosage regimens.

The single-dose regimen will be the choice from the standpoint of convenience unless it poses any particular concern. However, the 2-dose regimen may be more convenient than the single-dose regimen, for instance, at nursing homes for the elderly. Care-receiving elderly individuals may need assistance or guidance of a caregiver if having difficulty in inhaling the drug or taking longer time to empty a whole container. The-2-dose regimen (2 divided doses on separate days) will reduce the burden on both caregivers and care-receivers.

PMDA concluded that the applicant's explanation is acceptable.

7.R.5 Clinical positioning

The applicant's explanation on the clinical positioning of laninamivir octanoate:

Prophylaxis of influenza virus infection is generally classified into 2 ways: seasonal influenza vaccination for the prophylaxis of infection and post-exposure prophylaxis with an influenza antiviral drug. While vaccination is the primary preventive measure against infection, one of the disadvantages of vaccination is a possible mismatch between the available vaccine strains and the circulating strains (*The Journal of Japan Physicians Association*. 2011;26:15-21). Mismatched strains may reduce vaccine efficacy. If reduced vaccine efficacy is anticipated, post-exposure prophylaxis with influenza antiviral drugs should be beneficial for individuals who are at an increased risk of influenza infection. In particular, the elderly and those who have chronic respiratory or chronic heart disease are at a high risk of disease aggravation when infected with an influenza virus (Proposal of the Japanese Association for Infectious Diseases 2012: On the measures against nosocomial influenza infection [including infection in nursing homes]) http://www.kansensho.or.jp/guidelines/pdf/1208_teigen.pdf [March 2016]), warranting prophylactic measures against influenza virus infection.

The clinical studies were conducted in family or household contacts of patients with influenza A or B virus infection. The studies have demonstrated the safety and efficacy of a single dose of inhaled laninamivir octanoate 40 mg in subjects aged ≥10 years and a single dose of inhaled laninamivir octanoate 20 mg in children aged <10 years for the prophylaxis of influenza virus infection. The 2-dose regimen of laninamivir octanoate 20 mg has already been approved for the prophylaxis of influenza virus infection in adults and children aged ≥10 years, but the proposed additional 40 mg single-dose regimen is expected to be more convenient. Also, the proposed dosage regimen can offer a new option for the prophylaxis of influenza virus infection in children <10 years, which is of great clinical significance.

PMDA's view:

While vaccination is the primary preventive measure against influenza virus infection, laninamivir octanoate can serve as a complement to influenza virus vaccines. In this regard, laninamivir octanoate is a new option with promising efficacy in the prophylaxis of influenza virus infection.

Unlike in therapeutic use, prophylactic influenza antiviral drugs are more likely to be used in unspecified populations without much consideration, and this may lead to an increase in the risk of the emergence of resistant virus strains. The prophylactic use of laninamivir octanoate should be limited to the high-risk populations because they are prone to serious complications when infected with influenza virus. Healthcare professionals should be further reminded of this, as stated in the current package insert.

7.R.6 Post-marketing investigations

The applicant's explanation:

Given the safety profiles of laninamivir octanoate for both the proposed and approved dosage regimens do not suggest any new safety concern, post-marketing data will be collected in the routine pharmacovigilance activities. Another post-marketing surveillance is not necessary for the proposed additional dosage and administration.

PMDA's conclusion:

The applicant's explanation is acceptable. There is little need to conduct another post-marketing surveillance immediately, and no additional pharmacovigilance activities or risk minimization activities are required in the risk management plan at present.

The above conclusion of PMDA will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1 and CTD 5.3.5.1-2) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of Review Report (1)

PMDA has concluded that the data submitted demonstrate the efficacy of a single dose of inhaled laninamivir octanoate 40 mg in adults and children aged ≥10 years and a single dose of inhaled laninamivir octanoate 20 mg in children aged <10 years for the "prophylaxis of influenza A or B virus infection" and acceptable safety in view of the benefits indicated by the data submitted. The proposed additional dosage regimen of single-dose inhalation is expected to improve convenience in the prophylaxis of influenza in adults and children aged ≥10 years. Also, the proposed dosage regimen for children aged <10 years is a new option for the prophylaxis of influenza virus infection. Thus, the new dosage regimens are of clinical significance.

PMDA has concluded that laninamivir octanoate may be approved if laninamivir octanoate is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

June 24, 2016

Product Submitted for Approval

Brand Name	Inavir Dry Powder Inhaler 20 mg
Non-proprietary Name	Laninamivir Octanoate Hydrate
Applicant	Daiichi Sankyo Company, Limited
Date of Application	October 7, 2015

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported the PMDA's conclusion on issues presented in the Review Report (1) ["7.R.1. Development history and efficacy of laninamivir octanoate," "7.R.2 Safety," "7.R.4 Dosage and administration," and "7.R.6 Post-marketing investigations"]. The following comment was raised from the expert advisors:

- Healthcare professionals should be provided with adequate information to ensure that the use of laninamivir octanoate for the prophylaxis of influenza virus infection is limited to populations who are at high risk for severe influenza symptoms or influenza-related complications.

In response to the comments of the expert advisors, PMDA instructed the applicant to remind healthcare professionals of limiting the use of laninamivir octanoate to the pre-defined high-risk populations. As per the advice in the "Precautions" section of the package insert, the prophylactic use of laninamivir octanoate, as a rule, is limited to populations who are at high risk for severe influenza symptoms or influenza-related complications.

2. Overall Evaluation

Based on the results of the above review, PMDA has concluded that the product may be approved with the following indications, dosage and administration. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until September 9, 2018).

Indication

Treatment and prophylaxis of influenza A or B virus infection

(No change)

Dosage and Administration

1. Therapeutic use

Adults:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose.

Children aged <10 years:

Laninamivir octanoate 20 mg is administered by inhalation as a single dose.

Children aged ≥10 years:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose.

2. Prophylactic use

Adults:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose. Alternatively, laninamivir octanoate 20 mg may be administered by inhalation once daily for 2 days.

Children aged <10 years:

Laninamivir octanoate 20 mg is administered by inhalation as a single dose.

Children aged ≥10 years:

Laninamivir octanoate 40 mg is administered by inhalation as a single dose. Alternatively, laninamivir octanoate 20 mg may be administered by inhalation once daily for 2 days.

(Underlines denote addition.)