הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 05.2013)

תאריך: 12.07.2016

שם תכשיר באנגלית ומספר הרישום: Kalydeco 150 mg 00-01-02-03 34269 89 153

שם בעל הרישום: ורטקס פרמאסוטיקלס (יו.קיי) לימיטד

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות

פרק בעלון	טקסט נוכחי	טקסט חדש
Undesirable effects	Summary of the safety profile The safety profile of Kalydeco is based on the pooled data from two double-blind placebo-controlled clinical studies conducted in 213 CF patients (109 received ivacaftor and 104 patients who received placebo up to 48 weeks) and who had a *G551D* mutation in the *CFTR* gene, and an 8-week, double-blind, placebo-controlled crossover study in 39 patients with CF who had a non-*G551D* gating (class III) mutation in the *CFTR* gene. The most common adverse reactions experienced by patients who received ivacaftor in the pooled placebo-controlled Phase 3 studies were abdominal pain (15.6% versus 12.5% on placebo), diarrhoea (12.8% versus 9.6% on placebo), dizziness (9.2% versus 1.0% on placebo), rash (12.8% versus 6.7% on placebo), upper respiratory tract reactions (including upper respiratory tract infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion and nasopharyngitis) (63.3% versus 50.0% on placebo), headache (23.9% versus 16.3% on placebo) and bacteria in sputum (7.3% versus 3.8% on placebo). One patient in the ivacaftor group reported a serious adverse reaction: abdominal pain. Tabulated list of adverse reactions Adverse reactions identified in patients who had a *G551D* mutation in at least one allele, age 6 years and older (pooled Phase 3 studies with 96 weeks	Summary of the safety profile ~~The safety profile of Kalydeco is based on the pooled data from two double-blind placebo-controlled clinical studies conducted in 213 CF patients (109 received ivacaftor and 104 patients who received placebo up to 48 weeks) and who had a *G551D* mutation in the *CFTR* gene, and an 8-week, double-blind, placebo-controlled crossover study in 39 patients with CF who had a non-*G551D* gating (class III) mutation in the *CFTR* gene.~~ ~~The most common adverse reactions experienced by patients who received ivacaftor in the pooled placebo-controlled Phase 3 studies were abdominal pain (15.6% versus 12.5% on placebo), diarrhoea (12.8% versus 9.6% on placebo), dizziness (9.2% versus 1.0% on placebo), rash (12.8% versus 6.7% on placebo), upper respiratory tract reactions (including upper respiratory tract infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion and nasopharyngitis) (63.3% versus 50.0% on placebo), headache (23.9% versus 16.3% on placebo) and bacteria in sputum (7.3% versus 3.8% on placebo). One patient in the ivacaftor group reported a serious adverse reaction: abdominal pain.~~ The most common adverse reactions experienced by patients aged 6 years and older who received ivacaftor in the pooled 48-week placebo-controlled Phase 3 studies that occurred with an incidence of at least 3% and up to 9% higher than in the placebo arm were headache (23.9%), oropharyngeal pain (22.0%), upper respiratory tract infection (22.0%), nasal congestion (20.2%), abdominal pain (15.6%), nasopharyngitis (14.7%), diarrhoea (12.8%), dizziness (9.2%), rash (12.8%) and bacteria in sputum (12.8%). Transaminase elevations occurred in 12.8% of ivacaftor-treated patients versus 11.5% of placebo-treated patients. Serious adverse reactions in patients who received ivacaftor included abdominal pain and transaminase elevations (see section 4.4). Tabulated list of adverse reactions Table 1 reflects the adverse reactions observed with ivacaftor in clinical trials (placebo-controlled and uncontrolled studies) in which the length of exposure to ivacaftor ranged from 16

weeks to 144 weeks. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

~~Adverse reactions identified in patients who had a *G551D* mutation in at least one allele, age 6 years and older (pooled Phase 3 studies with 96 weeks open-label extension) are presented in Table 1 and are listed by system organ class, preferred term, and frequency. Adverse reactions are ranked under the MedDRA frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (frequency cannot be estimated using the available data).~~

Table 1

1. Adverse reactions in ivacaftor-treated patients

d 6 years and older ~~with the *G551D* mutation in the *CFTR* gene~~

System organ class	**verse reactions**	**Frequency**
Hepatobiliary disorders	Transaminase elevations	very commor
Investigations	Bacteria in sputum	very commor

open-label extension) are presented in Table 1 and are listed by system organ class, preferred term, and frequency. Adverse reactions are ranked under the MedDRA frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (frequency cannot be estimated using the available data).

Table 1. Adverse reactions in ivacaftor-treated patien 6 years and older with the *G551D* mutation in the *CF* gene

System Or Class	**Frequency Ca**	**Adverse Reactions (Preferred term) Ivacaftor N=198**
Investigatio	common	Bacteria in sputum

Description of selected adverse reactions

~~*Rash*~~

~~During 48-week placebo-controlled clinical studies, the incidence of rash was 12.8% in Kalydeco-treated patients. Including data from all clinical trial and post-marketing data, most of these events were non-serious and most of these patients did not discontinue the treatment because of rash.~~

~~*Ear and labyrinth disorders*~~

~~During 48-week placebo-controlled clinical studies, the incidence of ear and labyrinth disorders was 9.2% in Kalydeco-treated patients. Most events were described as mild to moderate in severity, 1 event of ear pain was described as severe, none were serious and no patients discontinued treatment because of ear and labyrinth disorders.~~

~~*Nervous system disorders*~~

~~Headache~~

~~During 48-week placebo-controlled clinical studies, the incidence of headache was 23.9% in Kalydeco-treated patients. Including data from all clinical trial and post-marketing data, most of these events were non-serious and most of these patients did not discontinue the treatment because of headache.~~

~~Dizziness~~

Description of selected adverse reactions

Rash

During 48-week placebo-controlled clinical studies, the incidence of rash was 12.8% in Kalydeco-treated patients. Including data from all clinical trial and post-marketing data, most of these events were non-serious and most of these patients did not discontinue the treatment because of rash.

Ear and labyrinth disorders

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Nervous system disorders

Headache

During 48-week placebo-controlled clinical studies, the incidence of headache was 23.9% in Kalydeco-treated patients. Including data from all clinical trial and post-marketing data, most of these events were non-serious and most of these patients did not discontinue the treatment because of headache.

During 48-week placebo-controlled clinical studies, the incidence of dizziness was 9.2% in the Kalydeco-treated patients. Including data from all clinical trial and post-marketing data, most of these events were non-serious and most of these patients did not discontinue the treatment because of dizziness.

Upper respiratory tract reactions
During 48-week placebo-controlled clinical studies, the incidence of upper respiratory tract reactions (upper respiratory tract infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion, and nasopharyngitis) was 63.3% in Kalydeco-treated patients. Most events were described as mild to moderate in severity, 1 event of upper respiratory tract infection and 1 event of nasal congestion were considered to be severe, none were serious, and no patients discontinued treatment because of upper respiratory tract reactions.

Paediatric population

Table 2 lists the adverse reactions by system organ class, preferred term, and frequency in Kalydeco-treated paediatric patients age 6 through to 17 in the pooled 48-week Phase 3 studies with 96 weeks open-label extension in patients with CF with a *G551D* mutation. The safety data are limited to 44 patients between 6 to 11 years of age, and 38 patients between 12 to 17 years of age. Adverse reactions are ranked under the MedDRA frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and unknown (frequency cannot be estimated using the available data).

Table 2.
Adverse reactions in ivacaftor-patients age 6 through 17 years with the *G551D* mutation in the *CFTR* gene

n Organ Class	Frequency Category		se Reactions r (Preferred Term)
	11 Years N=44	17 Years N=38	
Infections and infestations	very common	very common	Nasopharyngitis
	very common	very common	espiratory tract infection
	common	very common	Rhinitis
Nervous system disorders	very common	very common	Headache
	common	very common	Dizziness
ar and labyrinth	common	common	Ear pain

Dizziness
During 48-week placebo-controlled clinical studies, the incidence of dizziness was 9.2% in the Kalydeco-treated patients. Including data from all clinical trial and post-marketing data, most of these events were non-serious and most of these patients did not discontinue the treatment because of dizziness.

Upper respiratory tract reactions
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disorders	common	not observed	anic membrane hyperaemia
	common	not observed	Tinnitus
atory, thoracic,	very common	very common	asal congestion
and mediastinal	very common	very common	pharyngeal pain
disorders	common	not observed	ngeal erythema
	common	common	inus congestion
Gastrointestinal	very common	very common	Abdominal pain
disorders	very common	very common	Diarrhoea
d subcutaneous	common	very common	Rash
tissue disorders			
oductive system	not observed	common	Breast mass
breast disorders			
Investigations	very common	very common	n sputum

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breast disorders			
Investigations	very common	very common	teria in sputum

The safety data were evaluated in 61 patients between 6 to less than 12 years of age and 94 patients between 12 to less than 18 years of age.

The safety profile is generally consistent among children and adolescents and is also consistent with adult patients.

In children aged 6 to less than 12 years, the incidence of patients experiencing transaminase elevations (ALT or AST) >3 x ULN was 15.0% (6/40) in ivacaftor-treated patients and 14.6% (6/41) in patients who received placebo. A single ivacaftor-treated patient (2.5%) in this age range had an elevation of ALT and AST >8 x ULN. Peak LFT (ALT or AST) elevations were generally higher in paediatric patients than in older patients. In almost all instances where dosing was interrupted for elevated transaminases and subsequently resumed, ivacaftor dosing was able to be resumed successfully (see section 4.4).

הודעה על החמרה (מידע בטיחות) בעלון לצרכן
(מעודכן 05.2013)

תאריך: 12.07.2016

שם תכשיר באנגלית ומספר הרישום: Kalydeco 150mg 153 89 34269 00-01-02-03

שם בעל הרישום : ***ורטקס פרמאסוטיקלס (יו.קיי) לימיטד***

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות

פרק בעלון	טקסט נוכחי	טקסט חדש
1. **תופעות לוואי**	**תופעות לוואי שכיחות מאוד (מופיעות ביותר ממשתמש אחד מעשרה):** • זיהום בדרכי הנשימה העליונות (הצטננות), כולל: ° כאב גרון ° גודש באף • כאב ראש • סחרחורת שלשול • פריחה **תופעות לוואי שכיחות (מופיעות ב-10-1 משתמשים מתוך 100):** • גודש בסינוסים • נזלת • שינוי בסוג החיידקים בליחה • כאב אוזניים • צלצולים באוזניים • אודם בתוך האוזן • גושים בשד	**תופעות לוואי שכיחות מאוד (מופיעות ביותר ממשתמש אחד מעשרה):** • זיהום בדרכי הנשימה העליונות (הצטננות), כולל: ° כאב גרון ° גודש באף • כאב ראש • סחרחורת שלשול • פריחה • שינוי בסוג החיידקים בליחה **תופעות לוואי שכיחות (מופיעות ב-10-1 משתמשים מתוך 100):** • גודש בסינוסים • נזלת • ~~שינוי בסוג החיידקים בליחה~~ • כאב אוזניים, אי נוחות באוזן • צלצולים באוזניים • אודם בתוך האוזן • גושים בשד