

16.01.2017

## Giotrif® (afatinib) 20,30,40,50 mg

### הרחבת התוויה ועדכון עלון

רופא/ה יקר/ה, רוקח/ת יקר/ה,  
חברת בורינגר אינגלהיים ישראל בע"מ מבקשת להודיעכם על הרחבת התוויה ועדכון בעלון לרופא אשר אושרו על ידי משרד הבריאות בדצמבר 2016.  
**לתכשיר נוספה התוויה לטיפול כמונתרפיה ב-Squamous cell carcinoma אשר התקדמה תוך כדי או לאחר טיפול כמותרפי.**

ההתוויות המעודכנות לתכשיר בישראל:

GIOTRIF as monotherapy is indicated for the treatment of :

- Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s);
- locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy.

העלון לרופא והעלון לצרכן המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות. כמו כן, ניתן לקבלם מודפסים על-ידי פנייה לבעל הרישום: בורינגר אינגלהיים ישראל בע"מ, רח' מדינת היהודים 89 הרצליה פיתוח, ובטלפון 09-9730500. השינויים בעלון מתוארים בעמודים הבאים.



בברכה,  
יסמין בן יוסף  
רוקחת ממונה, בורינגר אינגלהיים ישראל

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

GIOTRIF as monotherapy is indicated for the treatment of ~~Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s) (see section 5.1):~~

- ~~Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s);~~
- locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy (see section 5.1).

### 4.2 Posology and method of administration

...

#### Posology

##### *Dose escalation*

A dose escalation to a maximum of 50 mg/day may be considered in patients who tolerate a 40 mg/day ~~dose starting dose~~ (i.e. absence of diarrhoea, skin rash, stomatitis, and other adverse reactions with CTCAE Grade > 1) in the first ~~3 weeks cycle of treatment (21 days for EGFR mutation positive NSCLC and 28 days for squamous NSCLC)~~. The dose should not be escalated in any patients with a prior dose reduction. The maximum daily dose is 50 mg.

...

##### *Patients with renal impairment*

~~The safety, pharmacokinetics and efficacy of this medicinal product have not been studied in a dedicated trial in patients with renal impairment. Adjustments to the starting dose are not necessary in patients with mild or moderate renal impairment. Treatment in patients with severely impaired renal function (< 30 mL/min creatinine clearance) is not recommended (see section 5.2).~~

Exposure to afatinib was found to be increased in patients with moderate or severe renal impairment (see section 5.2). Adjustments to the starting dose are not necessary in patients with mild (eGFR 60-89 mL/min/1.73m<sup>2</sup>), moderate (eGFR 30-59 mL/min/1.73m<sup>2</sup>) or severe (eGFR 15-29 mL/min/1.73m<sup>2</sup>) renal impairment. Monitor patients with severe renal impairment (eGFR 15-29 mL/min/1.73m<sup>2</sup>) and adjust GIOTRIF dose if not tolerated.  
GIOTRIF treatment in patients with eGFR <15 mL/min/1.73m<sup>2</sup> or on dialysis is not recommended.

### 4.4 Special warnings and precautions for use

#### Skin related adverse events

...

Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome ~~- and toxic epidermal necrolysis~~. Treatment with this medicinal product should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions (see section 4.8).

...

#### Severe hepatic impairment

Hepatic failure, including fatalities, has been reported during treatment with this medicinal product in less than 1% of patients. In these patients, confounding factors have included pre-existing liver disease and/or comorbidities associated with progression of underlying malignancy. Periodic liver function testing is

Formatted

Formatted

Formatted:

recommended in patients with pre-existing liver disease. In the pivotal trials Grade 3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were observed in 2.4% (LUX-Lung-3) and 1.6% (LUX-Lung 8) of patients with normal baseline liver tests treated with 40 mg/day; and, In LUX-Lung-3 Grade 3 ALT/AST elevations were about 3.5 fold higher in patients with abnormal baseline liver tests. There were no Grade 3 ALT/AST elevations in patients with abnormal baseline liver tests in LUX-Lung 8 (see section 4.8). Dose interruption may become necessary in patients who experience worsening of liver function (see section 4.2). In patients who develop severe hepatic impairment while taking GIOTRIF, treatment should be discontinued.

#### 4.8 Undesirable effects

##### Summary of the safety profile

...

In patients treated with once daily GIOTRIF 40 mg, dose reductions due to ADRs occurred in 57% of the patients in the LUX-Lung 3 trial and in 25% of the patients in the LUX-Lung 8 trial. Discontinuation due to ADRs diarrhoea and rash/acne was 1.3% and 0%; in LUX-Lung 3 and 3.8% and 2.0% in LUX-Lung 8, respectively.

ILD-like adverse reactions were reported in 0.7% of afatinib treated patients. Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome and toxic epidermal necrolysis although in these cases there were potential alternative aetiologies (see section 4.4).

##### Tabulated list of adverse reactions

Table 2 summarises the frequencies of ADRs ~~pooled~~ from all NSCLC trials and from post-marketing experience with daily GIOTRIF doses of 40 mg (~~N=497~~) or 50 mg (~~N=1638~~) as monotherapy. The following terms are used to rank the ADRs by frequency: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

...

New adverse events;

- **Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ):**
  - o Pancreatitis
- **Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ):**
  - o Stevens-Johnson syndrome<sup>7</sup>
  - o Toxic epidermal necrolysis<sup>7</sup>

...

Table 4: Very common ADRs in trial LUX-Lung 7

	<b><u>GIOTRIF</u></b> <b><u>(40 mg/day)</u></b> <b><u>N=160</u></b>			<b><u>Gefitinib</u></b> <b><u>N=159</u></b>		
<b><u>NCI-CTC Grade</u></b>	<b><u>Any</u></b> <b><u>Grade</u></b>	<b><u>3</u></b>	<b><u>4</u></b>	<b><u>Any</u></b> <b><u>Grade</u></b>	<b><u>3</u></b>	<b><u>4</u></b>
<b><u>MedDRA Preferred Term</u></b>	<b><u>%</u></b>	<b><u>%</u></b>	<b><u>%</u></b>	<b><u>%</u></b>	<b><u>%</u></b>	<b><u>%</u></b>
<b><u>Infections and infestations</u></b>						
<b><u>Paronychia<sup>1</sup></u></b>	<b><u>57.5</u></b>	<b><u>1.9</u></b>	<b><u>0</u></b>	<b><u>17.0</u></b>	<b><u>0.6</u></b>	<b><u>0</u></b>
<b><u>Cystitis<sup>2</sup></u></b>	<b><u>11.3</u></b>	<b><u>1.3</u></b>	<b><u>0</u></b>	<b><u>7.5</u></b>	<b><u>1.3</u></b>	<b><u>0.6</u></b>
<b><u>Metabolism and nutrition disorders</u></b>						
<b><u>Decreased appetite</u></b>	<b><u>27.5</u></b>	<b><u>1.3</u></b>	<b><u>0</u></b>	<b><u>24.5</u></b>	<b><u>1.9</u></b>	<b><u>0</u></b>
<b><u>Hypokalaemia<sup>3</sup></u></b>	<b><u>10.6</u></b>	<b><u>2.5</u></b>	<b><u>1.3</u></b>	<b><u>5.7</u></b>	<b><u>1.3</u></b>	<b><u>0</u></b>
<b><u>Respiratory, thoracic and mediastinal disorders</u></b>						
<b><u>Rhinorrhoea<sup>4</sup></u></b>	<b><u>19.4</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>7.5</u></b>	<b><u>0</u></b>	<b><u>0</u></b>
<b><u>Epistaxis</u></b>	<b><u>18.1</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>8.8</u></b>	<b><u>0</u></b>	<b><u>0</u></b>
<b><u>Gastrointestinal disorders</u></b>						
<b><u>Diarrhoea</u></b>	<b><u>90.6</u></b>	<b><u>13.8</u></b>	<b><u>0.6</u></b>	<b><u>64.2</u></b>	<b><u>3.1</u></b>	<b><u>0</u></b>
<b><u>Stomatitis<sup>5</sup></u></b>	<b><u>64.4</u></b>	<b><u>4.4</u></b>	<b><u>0</u></b>	<b><u>27.0</u></b>	<b><u>0</u></b>	<b><u>0</u></b>
<b><u>Nausea</u></b>	<b><u>25.6</u></b>	<b><u>1.3</u></b>	<b><u>0</u></b>	<b><u>27.7</u></b>	<b><u>1.3</u></b>	<b><u>0</u></b>
<b><u>Vomiting</u></b>	<b><u>19.4</u></b>	<b><u>0.6</u></b>	<b><u>0</u></b>	<b><u>13.8</u></b>	<b><u>2.5</u></b>	<b><u>0</u></b>
<b><u>Dyspepsia</u></b>	<b><u>10.0</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>8.2</u></b>	<b><u>0</u></b>	<b><u>0</u></b>
<b><u>Hepatobiliary disorders</u></b>						
<b><u>Alanine aminotransferase increased</u></b>	<b><u>11.3</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>27.7</u></b>	<b><u>8.8</u></b>	<b><u>0.6</u></b>
<b><u>Skin and subcutaneous tissue disorders</u></b>						
<b><u>Rash<sup>6</sup></u></b>	<b><u>80.0</u></b>	<b><u>7.5</u></b>	<b><u>0</u></b>	<b><u>67.9</u></b>	<b><u>3.1</u></b>	<b><u>0</u></b>
<b><u>Dry skin</u></b>	<b><u>32.5</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>39.6</u></b>	<b><u>0</u></b>	<b><u>0</u></b>
<b><u>Pruritus<sup>7</sup></u></b>	<b><u>25.6</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>25.2</u></b>	<b><u>0</u></b>	<b><u>0</u></b>
<b><u>Dermatitis acneiform<sup>8</sup></u></b>	<b><u>23.8</u></b>	<b><u>1.9</u></b>	<b><u>0</u></b>	<b><u>32.1</u></b>	<b><u>0.6</u></b>	<b><u>0</u></b>
<b><u>General disorders and administration site conditions</u></b>						
<b><u>Pyrexia</u></b>	<b><u>13.8</u></b>	<b><u>0</u></b>	<b><u>0</u></b>	<b><u>6.3</u></b>	<b><u>0</u></b>	<b><u>0</u></b>
<b><u>Investigations</u></b>						
<b><u>Weight decreased</u></b>	<b><u>10.0</u></b>	<b><u>0.6</u></b>	<b><u>0</u></b>	<b><u>5.7</u></b>	<b><u>0.6</u></b>	<b><u>0</u></b>

<sup>1</sup> Includes Paronychia, Nail infection, Nail bed infection

<sup>2</sup> Includes Cystitis, Urinary tract infection

<sup>3</sup> Includes Hypokalaemia, Blood potassium decreased

<sup>4</sup> Includes Rhinorrhoea, Nasal inflammation

<sup>5</sup> Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Mucosal erosion

<sup>6</sup> Includes group of rash preferred terms

<sup>7</sup> Includes Pruritus, Pruritus generalised

<sup>8</sup> Includes Dermatitis acneiform, Acne

Formatted:  
10 pt, English

## Description of selected adverse reactions

Very common ADRs in GIOTRIF-treated patients occurring in at least 10% of patients in trial LUX-Lung 8 are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 5.

Table 5: Very common ADRs in trial LUX-Lung 8\*

	<u>GIOTRIF</u> <u>(40 mg/day)</u> <u>N=392</u>			<u>Erlotinib</u> <u>N=395</u>		
<u>NCI-CTC Grade</u>	<u>Any</u> <u>Grade</u>	<u>3</u>	<u>4</u>	<u>Any</u> <u>Grade</u>	<u>3</u>	<u>4</u>
<u>MedDRA Preferred Term</u>	<u>%</u>	<u>%</u>	<u>%</u>	<u>%</u>	<u>%</u>	<u>%</u>
<u>Infections and infestations</u>						
<u>Paronychia<sup>1</sup></u>	<u>11.0</u>	<u>0.5</u>	<u>0</u>	<u>5.1</u>	<u>0.3</u>	<u>0</u>
<u>Metabolism and nutrition disorders</u>						
<u>Decreased appetite</u>	<u>24.7</u>	<u>3.1</u>	<u>0</u>	<u>26.1</u>	<u>2.0</u>	<u>0</u>
<u>Gastrointestinal disorders</u>						
<u>Diarrhoea</u>	<u>74.7</u>	<u>9.9</u>	<u>0.8</u>	<u>41.3</u>	<u>3.0</u>	<u>0.3</u>
<u>Stomatitis<sup>2</sup></u>	<u>30.1</u>	<u>4.1</u>	<u>0</u>	<u>10.6</u>	<u>0.5</u>	<u>0</u>
<u>Nausea</u>	<u>20.7</u>	<u>1.5</u>	<u>0</u>	<u>16.2</u>	<u>1.0</u>	<u>0.3</u>
<u>Skin and subcutaneous tissue disorders</u>						
<u>Rash<sup>3</sup></u>	<u>60.7</u>	<u>5.4</u>	<u>0</u>	<u>56.7</u>	<u>8.1</u>	<u>0</u>
<u>Dermatitis acneiform<sup>4</sup></u>	<u>14.0</u>	<u>1.3</u>	<u>0</u>	<u>18.0</u>	<u>2.5</u>	<u>0</u>

\* Reporting the frequency of patients with all causality AEs

<sup>1</sup> Includes Paronychia, Nail infection, Nail bed infection

<sup>2</sup> Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Oral mucosa erosion, Mucosal erosion, Mucosal ulceration

<sup>3</sup> Includes group of rash preferred terms

<sup>4</sup> Includes Acne, Acne pustular, Dermatitis acneiform

## Liver function test abnormalities

Liver function test abnormalities (including elevated ALT and AST) were observed in patients receiving GIOTRIF 40 mg. These elevations were mainly transient and did not lead to discontinuation. Grade 2 ALT elevations occurred in 1% and Grade 3 elevations occurred in 0.8% of patients treated with GIOTRIF (see section 4.4).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

#### Clinical efficacy and safety

##### LUX-Lung 7

LUX-Lung 7 is a randomised, global, open label Phase IIb trial investigating the efficacy and safety of GIOTRIF in patients with locally advanced or metastatic lung adenocarcinoma (stage IIIB or IV) with EGFR mutations in the first-line setting. Patients were screened for the presence of activating EGFR mutations (Del 19 and/or L858R) using the TheraScreen<sup>®</sup> EGFR RGQ PCR Kit, Qiagen Manchester Ltd). Patients (N=319) were randomised (1:1) to receive GIOTRIF<sup>®</sup> 40 mg orally once daily (N=160) or gefitinib 250 mg orally once daily (N=159). Randomisation was stratified according to EGFR mutation status (Del 19; L858R) and presence of brain metastases (yes; no).

Among the patients randomised, 62% were female, the median age was 63 years, 16% of patients had brain metastases, the baseline ECOG performance status was 0 (31%) or 1 (69%), 57% were Asian and 43% were non-Asian. Patients had a tumour sample with an EGFR mutation categorised as either exon 19 deletion (58%) or exon 21 L858R substitutions (42%).

The co-primary endpoints include PFS by independent review and OS. Secondary endpoints include ORR and DCR. GIOTRIF significantly improved PFS and ORR in EGFR mutation positive patients compared to gefitinib. The efficacy results are summarized in Table 9.

Table 9: Efficacy results of GIOTRIF vs. gefitinib (LUX-Lung 7) based on primary analysis as of August 2015.

	<b><u>GIOTRIF</u></b> <b><u>(N=160)</u></b>	<b><u>Gefitinib</u></b> <b><u>(N=159)</u></b>	<b><u>Hazard Ratio/ Odds Ratio</u></b> <b><u>(95%CI)</u></b> <b><u>p-value<sup>2</sup></u></b>
<b><u>Median PFS (months), Overall Trial Population</u></b>	<u>11.0</u>	<u>10.9</u>	<u>HR 0.73</u> <u>(0.57-0.95)</u> <u>0.0165</u>
<b><u>18-months PFS rate</u></b>	<u>27%</u>	<u>15%</u>	
<b><u>24-months PFS rate</u></b>	<u>18%</u>	<u>8%</u>	
<b><u>Median OS (months)<sup>1</sup>, Overall Trial Population</u></b>	<u>27.9</u>	<u>24.5</u>	<u>HR 0.86</u> <u>(0.66, 1.12)</u> <u>0.2580</u>
<b><u>Alive at 18-months</u></b>	<u>71%</u>	<u>67%</u>	
<b><u>Alive at 24-months</u></b>	<u>61%</u>	<u>51%</u>	
<b><u>Objective Response Rate (CR+PR)<sup>3</sup></u></b>	<u>70%</u>	<u>56%</u>	<u>OR 1.87</u> <u>(1.12, 2.99)</u> <u>0.0083</u>

<sup>1</sup>OS results based on primary OS analysis as of April 2016 at event rates of 109 (68.1%) and 117 (73.6%) in the GIOTRIF and gefitinib arms, respectively

<sup>2</sup>p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate based on stratified logistic regression

<sup>3</sup>CR=complete response; PR=partial response

The PFS hazard ratio for patients with DEL 19 mutations and L858R mutations was 0.76 (95% CI [0.55, 1.06]; p=0.1071), and 0.71 (95% CI [0.47, 1.06]; p=0.0856) respectively for afatinib vs gefitinib.

#### GIOTRIF in patients with NSCLC of squamous histology

The efficacy and safety of GIOTRIF as second-line treatment for patients with advanced NSCLC of squamous histology was investigated in a randomized open-label global Phase III trial LUX-Lung 8. Patients who received at least 4 cycles of platinum-based therapy in the first line setting were subsequently randomized 1:1 to daily GIOTRIF 40 mg or erlotinib 150 mg until progression. Randomization was stratified by race (Eastern Asian vs non Eastern Asian). The primary endpoint was PFS; OS was the key secondary endpoint. Other secondary endpoints included ORR, DCR, change in tumour size and HRQOL.

Among 795 patients randomized, the majority were males (84%), white (73%), current or former smokers (95%) with baseline performance status ECOG 1 (67%) and ECOG 0 (33%).

Second-line GIOTRIF significantly improved PFS and OS of patients with squamous NSCLC compared to erlotinib. The efficacy results at the time of the primary analysis of OS including all randomized patients are summarized in Figure 2 and Table 10.

Table 10: Efficacy results for GIOTRIF vs erlotinib in LUX-Lung 8, based on primary analysis of OS, including all randomized patients

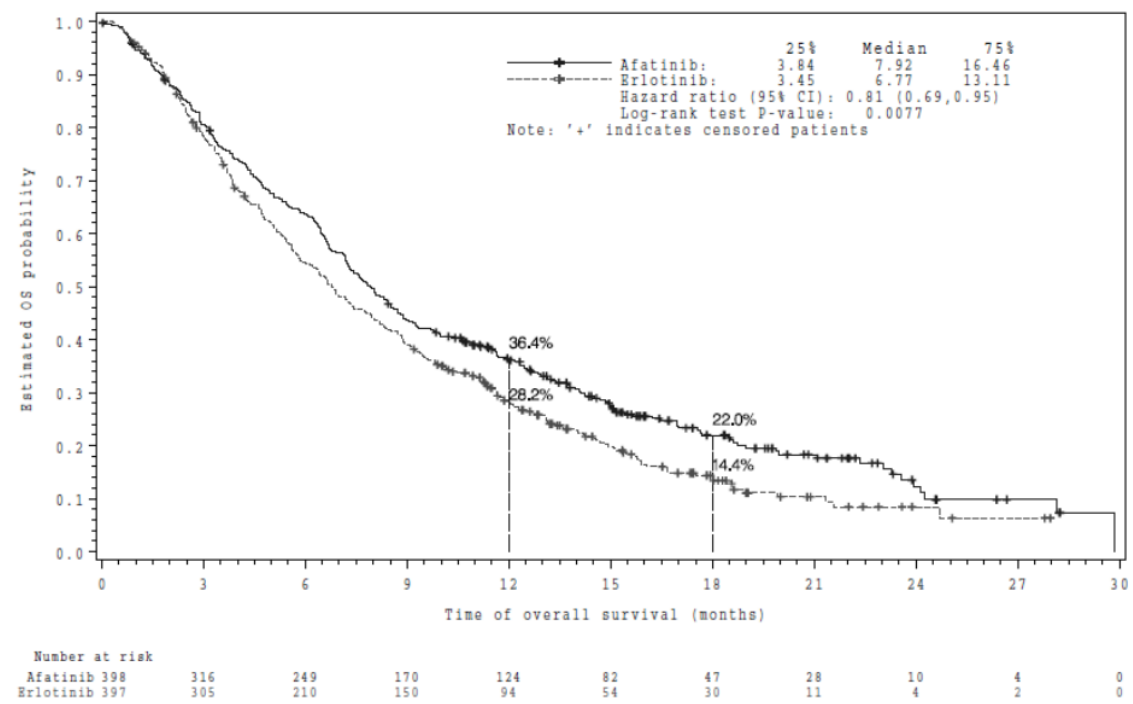
	<b><u>GIOTRIF</u></b> <b><u>(N=398)</u></b>	<b><u>Erlotinib</u></b> <b><u>(n=397)</u></b>	<b><u>Hazard Ratio/ Odds Ratio</u></b> <b><u>(95%CI)</u></b>	<b><u>p-value<sup>2</sup></u></b>
<b><u>PFS</u></b>				
<b><u>Months (median)</u></b>	<b><u>2.63</u></b>	<b><u>1.94</u></b>	<b><u>HR 0.81</u></b> <b><u>(0.69, 0.96)</u></b>	<b><u>0.0103</u></b>
<b><u>OS</u></b>				
<b><u>Months (median)</u></b>	<b><u>7.92</u></b>	<b><u>6.77</u></b>	<b><u>HR 0.81</u></b> <b><u>(0.69, 0.95)</u></b>	<b><u>0.0077</u></b>
<b><u>Alive at 12 months</u></b>	<b><u>36.4%</u></b>	<b><u>28.2%</u></b>		
<b><u>Alive at 18 months</u></b>	<b><u>22.0%</u></b>	<b><u>14.4%</u></b>		
<b><u>Objective Response</u></b> <b><u>Rate (CR+PR)<sup>1</sup></u></b>	<b><u>5.5%</u></b>	<b><u>2.8%</u></b>	<b><u>OR 2.06</u></b> <b><u>(0.98, 4.32)</u></b>	<b><u>0.0551</u></b>
<b><u>Duration of response</u></b> <b><u>Months (median)</u></b>	<b><u>7.29</u></b>	<b><u>3.71</u></b>		

<sup>1</sup>CR=complete response; PR=partial response

<sup>2</sup>p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate based on logistic regression

The overall survival hazard ratio in patients < 65 years of age was 0.68 (95% CI 0.55, 0.85) and in patients 65 years of age and older it was 0.95 (95% CI 0.76, 1.19).

Figure 2: Kaplan-Meier Curve for OS by treatment group in LUX Lung 8



PFS benefit was accompanied by improvement in disease-related symptoms and delayed time to deterioration (see Table 11).

Table 11: Symptom outcomes for GIOTRIF vs. erlotinib in trial LUX-Lung 8 (EORTC QLQ-C30 & QLQ-LC13)

	<u>Cough</u>	<u>Dyspnoea</u>	<u>Pain</u>
<u>% of patients improved<sup>a, c</sup></u>	<u>43% vs. 35%;</u> <u>p=0.0294</u>	<u>51% vs. 44%;</u> <u>p=0.0605</u>	<u>40% vs. 39%;</u> <u>p=0.7752</u>
<u>Delay of time to deterioration (months)<sup>b, c</sup></u>	<u>4.5 vs. 3.7</u> <u>HR 0.89; p=0.2562</u>	<u>2.6 vs. 1.9</u> <u>HR 0.79; p=0.0078</u>	<u>2.5 vs. 2.4</u> <u>HR 0.99; p=0.8690</u>

<sup>a</sup> values presented for GIOTRIF vs. erlotinib, p-value based on logistic regression

<sup>b</sup> p-value for time to deterioration based on stratified log-rank test

<sup>c</sup> p-values were not adjusted for multiplicity

Efficacy in EGFR-negative tumours has not been established.

...

## **5.2 Pharmacokinetic properties**

...

### Special populations

#### Renal impairment

Less than 5% of a single dose of afatinib is excreted via the kidneys. The safety, pharmacokinetics and efficacy of GIOTRIF have not been studied specifically in patients with renal impairment. Based on population pharmacokinetic data derived from clinical trials in various tumour types, no dose adjustments appear necessary in patients with mild or moderate renal impairment (see “Population pharmacokinetic analysis in special populations” below and section 4.2).

Less than 5% of a single dose of afatinib is excreted via the kidneys. Exposure to afatinib in subjects with renal impairment was compared to healthy volunteers following a single dose of 40 mg GIOTRIF. Subjects with moderate renal impairment (n=8; eGFR 30-59 mL/min/1.73m<sup>2</sup>, according to the Modification of Diet in Renal Disease [MDRD] formula) had an exposure of 101% (C<sub>max</sub>) and 122% (AUC<sub>0-tz</sub>) in comparison to their healthy controls. Subjects with severe renal impairment (n=8; eGFR 15-29 mL/min/1.73m<sup>2</sup>, according to the MDRD formula) had an exposure of 122% (C<sub>max</sub>) and 150% (AUC<sub>0-tz</sub>) in comparison to their healthy controls. Based on this trial and population pharmacokinetic analysis of data derived from clinical trials in various tumour types, it is concluded, that adjustments to the starting dose in patients with mild (eGFR 60-89 mL/min/1.73m<sup>2</sup>), moderate (eGFR 30-59 mL/min/1.73m<sup>2</sup>), or severe (eGFR 15-29 mL/min/1.73m<sup>2</sup>) renal impairment are not necessary, but patients with severe impairment should be monitored (see “Population pharmacokinetic analysis in special populations” below and section 4.2). GIOTRIF has not been studied in patients with eGFR <15 mL/min/1.73m<sup>2</sup> or on dialysis.

## **1. למה מיועדת התרופה?**

- התרופה משמשת כטיפול יחיד (מונותרפיה) לטיפול ב: חולים מבוגרים הסובלים מסרטן ריאה של תאים שאינם קטנים (NSCLC), המאופיינים על-ידי מוטציה בגן EGFR (Epidermal Growth Factor Receptor).  
אשר מחלתם נמצאת בשלב מתקדם מקומי או גרורתי וטרם טופלו במעכבי טירוזין קינאז לרצפטור EGFR.

- חולים מבוגרים הסובלים מסרטן הריאה של תאים שאינם קטנים (NSCLC) ממקור תאי קשקש (squamous), אשר מחלתם נמצאת בשלב מתקדם מקומי או גרורתי והתקדמה תוך כדי או לאחר טיפול כמותרפי.

## **2. לפני שימוש בתרופה**

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

- יש להיוועץ ברופא או ברוקח לפני התחלת הטיפול בתרופה:
  - אם משקל גופך פחות מ-50 ק"ג, או אם את אישה או אם הינך סובל מבעיות כליה. אם אחד מקריטריונים אלו חלים עליך, ייתכן ותצטרך להיות תחת השגחה הדוקה יותר של הרופא המטפל. במקרים אלו, תופעות הלוואי עשויות להיות חריפות יותר. התרופה אינה מומלצת אם יש לך מחלת כליה-חמורה.
  - אם אתה משתמש בעדשות מגע ו/או יש לך היסטוריה של בעיות עיניים כמו יובש חמור בעיניים, דלקת של החלק החיצוני של העין (קרנית) או כיבים בעין הכוללים את הקרנית-החלק החיצוני של העין.

**תופעות לוואי שכיחות מאוד (עשויות להופיע בקרב יותר ממשתמש אחד מתוך 10):**

- יובש וגירודים בעור

**תופעות לוואי שאינן שכיחות (עשויות להופיע עד 1-10 משתמשים מתוך 1,000):**

- דלקת בלבלב

**תופעות לוואי נדירות (עשויות להופיע עד למשתמש אחד מתוך 1,000):**

- מצב חמור של שלפוחיות בעור או קילוף של העור (עלול לרמז על תסמונת סטיבנס-ג'ונסון ונמק אפידרמי רעלני (toxic epidermal necrolysis)).