

AFATINIB*

B A C K G R O U N D E R

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2. How does afatinib work?
3. Data overview: the LUX-Lung clinical trial programme
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1. WHAT IS AFATINIB?

Afatinib is an irreversible [ErbB Family](#) blocker approved in [more than 70 markets](#). It is indicated for the treatment of patients with distinct types of epidermal growth factor receptor *EGFR* mutation-positive (*EGFR* M+) locally advanced or metastatic [non-small cell lung cancer \(NSCLC\)](#), and for the treatment of patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy. It is an oral, once-daily, targeted therapy.¹

2. HOW DOES AFATINIB WORK?

[Afatinib](#) selectively, potently and irreversibly binds to and blocks EGFR (ErbB1), HER2 (ErbB2) and ErbB4. In doing so, afatinib blocks downstream signalling from all homo- and heterodimers formed by ErbB Family members that are known to play a critical role in the growth and spread of the most widespread cancers and cancers associated with high mortality.^{2,3,4} This family of receptors is often overexpressed or mutated in many cancers (including lung, breast, head and neck, bladder, pancreatic and colorectal cancers), and is involved in fundamental processes such as cell proliferation, survival, invasion, and differentiation.^{5,6}

The irreversible binding of afatinib is unlike reversible compounds, as it aims to provide sustained, selective and complete blockade of ErbB Family members. Afatinib's mechanism of action has a positive effect on the tumour, preventing tumour cell growth and spread across a broad range of cancers, compared with other treatments that offer single, reversible receptor blocking (Figure 1).^{2,3,4}

*Afatinib is approved in more than 70 markets including the EU, Japan, Taiwan, and Canada under the brand name GIOTRIF[®], in the US under the brand name GILOTRIF[®] and in India under the brand name Xovoltib[®]; for the full list please see here.

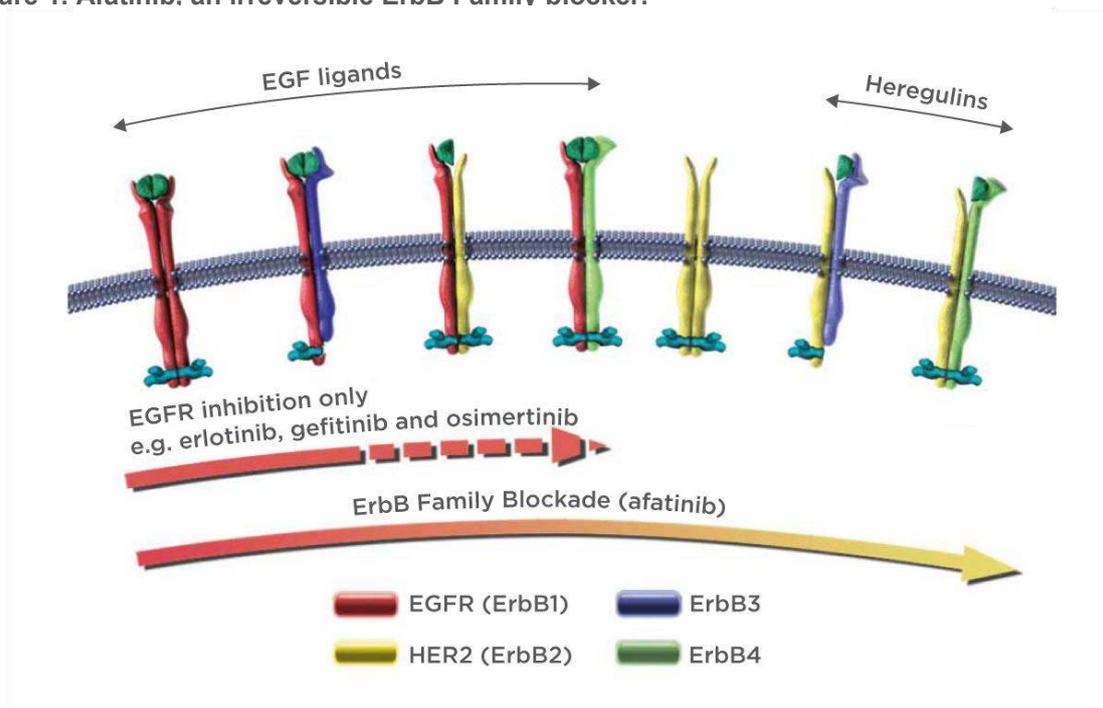
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Information on this website is derived from the approved European Summary of Product Characteristics. Please refer to your local product label for full details.

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Figure 1. Afatinib, an irreversible ErbB Family blocker.



3. DATA OVERVIEW: THE LUX-LUNG CLINICAL TRIAL PROGRAMME

The LUX-Lung clinical trial programme comprises eight studies investigating afatinib in a number of patient populations with advanced NSCLC. A brief overview of the trials is provided in **Table 1**.

It includes two pivotal Phase III studies, [LUX-Lung 3](#)^{7,8} and [LUX-Lung 6](#)^{9,10}.

[LUX-Lung 7](#) was the first global head-to-head trial comparing second- with first-generation EGFR-targeting agents (afatinib and gefitinib, respectively) in 1st-line EGFR M+ NSCLC.¹¹ [LUX-Lung 8](#) directly compared the efficacy of two EGFR targeting compounds, afatinib vs erlotinib, in patients with advanced squamous cell carcinoma (SqCC) of the lung.¹²



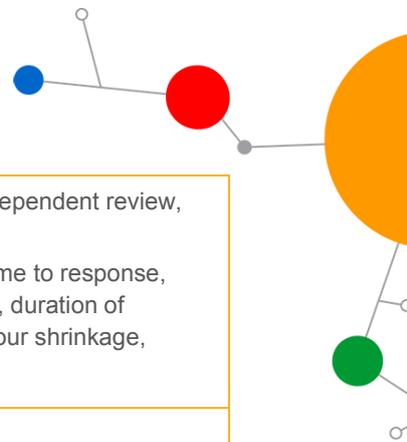
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Table 1. An overview of the LUX-Lung trial programme for afatinib in NSCLC.

LUX-Lung trial	Methods overview	Endpoints overview
LUX-Lung 1 ¹³ CT.gov identifier: NCT00656136	Phase IIb/III Randomised, double-blind Afatinib plus BSC vs placebo plus BSC Patients with NSCLC failing erlotinib or gefitinib	Primary: OS Secondary: PFS, ORR
LUX-Lung 2 ¹⁴ CT.gov identifier: NCT00525148	Phase II Open-label trial Continuous once-daily, oral treatment with afatinib Patients with Stage IIIB or IV lung adenocarcinoma with an <i>EGFR</i> -activating mutation	Primary: ORR (CR or PR) Secondary: PFS, OS
LUX-Lung 3 ^{7,8} CT.gov identifier: NCT00949650	Phase III Randomised, open-label Afatinib vs chemotherapy as first-line treatment Patients with Stage IIIB or IV lung adenocarcinoma with an <i>EGFR</i> -activating mutation	Primary: PFS, assessed by independent review Secondary: ORR, percentage with DC, OS, ECOG PS change since baseline, DCR, HRQoL, pharmacokinetics
LUX-Lung 4 ¹⁵ CT.gov identifier: NCT00711594	Phase I/II Open-label trial Continuous, once-daily, oral treatment with afatinib Phase I: patients with advanced NSCLC Phase II: patients with NSCLC failing erlotinib or gefitinib	Phase I, primary: incidence of DLT, incidence and intensity of AEs Phase I, secondary: pharmacokinetics, summary of <i>EGFR</i> mutations Phase II, primary: ORR Phase II, secondary: DCR, time and duration of OR, duration of disease control, PFS, OS, trough plasma concentrations, summary of <i>EGFR</i> mutations
LUX-Lung 5 ¹⁶ CT.gov identifier: NCT01085136	Phase III Randomised trial Afatinib plus weekly paclitaxel vs investigator's choice of chemotherapy following afatinib monotherapy Patients with NSCLC failing previous erlotinib or gefitinib treatment	Primary: PFS Secondary: OS, ORR, HRQoL
LUX-Lung 6 ^{9,10} CT.gov identifier: NCT01121393	Phase III Randomised, open-label Afatinib vs chemotherapy as first-line treatment Patients with Stage IIIB or IV lung adenocarcinoma with an <i>EGFR</i> -activating mutation	Primary: PFS Secondary: OS, ORR, DCR, time to and duration of OR, duration of disease control, ECOG PS change since baseline, HRQoL, pharmacokinetics

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<p>LUX-Lung 7^{11,17} CT.gov identifier: NCT01466660</p>	<p>Phase IIb Randomised, open-label Afinib vs gefitinib as first-line treatment Patients with <i>EGFR</i> mutations (del19/L858R) and advanced adenocarcinoma of the lung</p>	<p>Primary: PFS by independent review, TTF, OS Secondary: ORR, time to response, duration of response, duration of disease control, tumour shrinkage, HRQoL</p>
<p>LUX-Lung 8¹² CT.gov identifier: NCT01523587</p>	<p>Phase III Randomised, open-label Afinib vs erlotinib as second-line therapy following first-line platinum-based chemotherapy Patients with advanced SqCC of the lung</p>	<p>Primary: PFS Secondary: OS, OR, DCR, tumour shrinkage, HRQoL</p>

AE, adverse event; BSC, best supportive care; CR, complete response; DC, disease control; DCR, disease control rate; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; NSCLC, non-small cell lung cancer; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SqCC, squamous cell carcinoma; TTF, time to treatment failure.

Afinib’s efficacy and safety profile

The LUX-Lung 3 and LUX-Lung 6 trials both met their primary endpoint of progression-free survival, as afinib significantly delayed tumour growth vs standard chemotherapy in patients with *EGFR* M+ NSCLC.^{7–10}

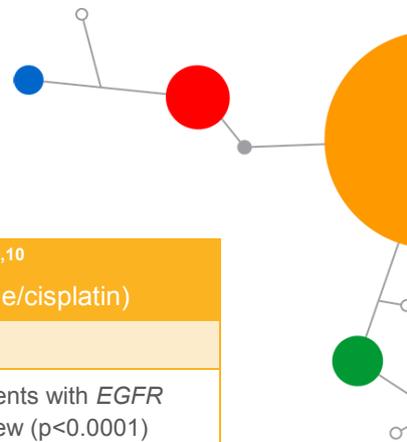
In a prespecified subgroup analysis, LUX-Lung 3 and LUX-Lung 6 independently demonstrated that afinib is the first treatment to show an overall survival benefit for patients with the most common type of *EGFR* mutation (del19). These patients lived a median of more than 1 year longer if they started treatment with afinib rather than standard chemotherapy.¹⁸

A combined exploratory analysis of the LUX-Lung 3 and LUX-Lung 6 trials demonstrated that afinib offered an overall survival benefit to patients whose tumours harbour common *EGFR* mutations (del19/L858R), as these patients lived for a median of 3 months longer compared with patients receiving standard chemotherapy.¹⁸ Afinib has also been shown to be active in NSCLC tumours harbouring certain types of uncommon mutations.^{18,19}

Post-hoc analysis of clinical outcomes in a combined data set from LUX-Lung 3 and LUX-Lung 6 trials showed the clinical activity of afinib in patients with *EGFR* M+ NSCLC and asymptomatic brain metastases.²⁰ Together, these data could help inform treatment decisions for patients with *EGFR* M+ NSCLC. Brief overviews of the LUX-Lung programme results are shown below.



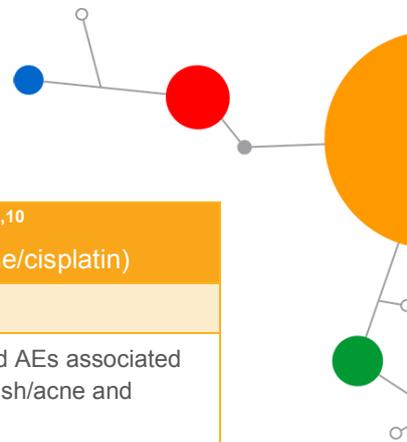
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LUX-Lung 3 ^{7,8} (afatinib vs pemetrexed/cisplatin)	LUX-Lung 6 ^{9,10} (afatinib vs gemcitabine/cisplatin)
PFS^{8,9} (primary endpoint)	
<ul style="list-style-type: none"> • 11.1 vs 6.9 months for all patients with <i>EGFR</i> mutations by independent review (p=0.001) • 13.6 vs 6.9 months for patients with the most common mutations (del19 and L858R; ~89% of all patients) by independent review (p=0.001) 	<ul style="list-style-type: none"> • 11.1 vs 5.6 months for all patients with <i>EGFR</i> mutations by independent review (p<0.0001) • Based on investigator review, patients lived for well over a year before their tumour started to grow again, vs just under half a year for those on standard chemotherapy (PFS of 13.7 vs 5.6 months, p<0.0001)
<ul style="list-style-type: none"> • The delay in tumour growth compared well in both trials, substantiating the efficacy of afatinib and the robustness of the data 	
OS¹⁸ (secondary endpoint)	
<ul style="list-style-type: none"> • Statistically significant improvement in OS, in patients with common mutations (del19/L858R), with afatinib compared with chemotherapy (median 27.3 vs 24.4 months, p=0.037) in the post-hoc analysis combining LUX-Lung 3 and LUX-Lung 6 	
<ul style="list-style-type: none"> • More than 1 year OS benefit (median 33.3 vs 21.1 months, p=0.0015) with afatinib in patients with the del19 mutation compared with chemotherapy in the prespecified subgroup analysis of LUX-Lung 3 	<ul style="list-style-type: none"> • More than 1 year OS benefit (median 31.4 vs 18.4 months, p=0.023) with afatinib in patients with the del19 mutation compared with chemotherapy in the prespecified subgroup analysis of LUX-Lung 6
<ul style="list-style-type: none"> • In the overall patient population for each individual study, there was no significant OS benefit of afatinib compared with chemotherapy (28.2 vs 28.2 months for LUX-Lung 3 and 23.1 vs 23.5 months for LUX-Lung 6) 	
ORR^{8,9} (tumour shrinkage, secondary endpoint)	
<ul style="list-style-type: none"> • Higher ORR was observed in patients taking afatinib (56%) compared with those receiving chemotherapy (23%), as assessed by independent review (p=0.001) 	<ul style="list-style-type: none"> • A greater proportion of patients receiving afatinib (66.9%) had an ORR compared with patients in the gemcitabine/cisplatin chemotherapy (23%) arm, as assessed by independent review (p<0.0001)
<ul style="list-style-type: none"> • Tumour shrinkage translated into improvements in disease-related symptoms 	
Disease-related symptoms^{7,10} (secondary endpoint)	
<ul style="list-style-type: none"> • In LUX-Lung 3 and LUX-Lung 6, more patients taking afatinib experienced improvement of symptoms such as dyspnoea, cough and chest pain. Afatinib treatment also delayed the onset of these symptoms 	
HRQoL^{7,10} (measured by patient questionnaires, secondary endpoint)	
<ul style="list-style-type: none"> • Patients taking afatinib in LUX-Lung 3 and LUX-Lung 6 were reported to have a significantly better HRQoL than those on chemotherapy (LUX-Lung 3, p=0.015; LUX-Lung 6, p<0.0001) 	



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LUX-Lung 3 ^{7,8} (afatinib vs pemetrexed/cisplatin)	LUX-Lung 6 ^{9,10} (afatinib vs gemcitabine/cisplatin)
Grade ≥3 AEs^{8,9}	
<ul style="list-style-type: none"> The most common drug-related AEs observed in the afatinib treatment arm were diarrhoea, rash and paronychia The most common drug-related AEs observed in the chemotherapy arm were nausea/vomiting, decreased appetite and fatigue There was a low discontinuation rate associated with treatment-related AEs in the trial (8% discontinuation rate for afatinib; 12% for chemotherapy) In the afatinib arm, only diarrhoea (1.3%) and paronychia (0.9%) resulted in treatment discontinuation 	<ul style="list-style-type: none"> The most common drug-related AEs associated with afatinib were diarrhoea, rash/acne and stomatitis/mucositis The most common AEs associated with chemotherapy were neutropenia, vomiting and leucopenia The discontinuation rate due to AEs was 6% of patients in the afatinib arm and 40% of patients in the chemotherapy arm

AE, adverse event; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; HRQoL, health-related quality of life.

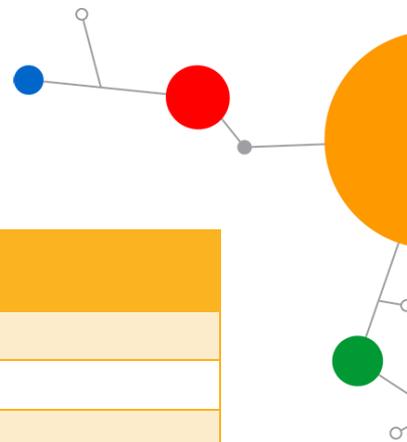
LUX-Lung 5 ¹⁶ (afatinib + paclitaxel vs investigators' choice of chemotherapy)
PFS (primary endpoint)
<ul style="list-style-type: none"> 5.6 vs 2.8 months (statistically significant, p=0.003)
OS (secondary endpoint)
<ul style="list-style-type: none"> OS was similar in both arms (12.2 vs 12.2 months, p=0.994)
ORR (secondary endpoint)
<ul style="list-style-type: none"> 32.1% of patients taking afatinib experienced tumour shrinkage compared with 13.2% in the chemotherapy arm (p=0.005) Tumour shrinkage translated into improvements in disease-related symptoms
AEs
<ul style="list-style-type: none"> The most common drug-related AEs observed in the afatinib treatment arm were diarrhoea (53.8%), alopecia (32.6%) asthenia (27.3%), decreased appetite (22.0%) and rash (20.5%)

AE, adverse event; OS, overall survival; ORR, objective response rate; PFS, progression-free survival.



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LUX-Lung 7 ^{11,17} (afatinib vs gefitinib)
PFS (primary endpoint)
<ul style="list-style-type: none"> 11.0 vs 10.9 months (statistically significant, p=0.017 by independent review)
TTF
<ul style="list-style-type: none"> 13.7 vs 11.5 months (p=0.007)
OS
<ul style="list-style-type: none"> Primary OS analysis: 27.9 vs 25.0 months (p=0.33) Mature OS analysis: 27.9 vs 24.5 months (p=0.258)
ORR (secondary endpoint)
<ul style="list-style-type: none"> 70% vs 56% (p=0.008)
AEs
<ul style="list-style-type: none"> AE profile was similar in both groups, with drug-related AEs leading to discontinuations occurring in 6.3% of patients in both treatment groups. The most common drug-related Grade 3 AEs were diarrhoea (11.9%), rash/acne (9.4%), fatigue (5.6%) and stomatitis (4.4%) in the afatinib group, while in the gefitinib group increased ALT (7.5%) and rash/acne (3.1%) were common

AE, adverse event; ALT, alanine aminotransferase; ORR, objective response rate; PFS, progression-free survival; TTF, time to treatment failure.

LUX-Lung 8 ¹² (afatinib vs erlotinib)
PFS (primary endpoint)
<ul style="list-style-type: none"> 2.4 vs 1.9 months (statistically significant, p=0.043 by independent review)
ORR (secondary endpoint)
<ul style="list-style-type: none"> 6.0% vs 3.0% (p=0.055)
DCR (secondary endpoint)
<ul style="list-style-type: none"> 51.0% vs 40.0% (statistically significant, p=0.0020)
HRQoL (secondary endpoint)
<ul style="list-style-type: none"> More patients had improved overall HRQoL with afatinib than with erlotinib (36% vs 28%, p=0.041)
OS (secondary endpoint)
<ul style="list-style-type: none"> OS was significantly greater in the afatinib group than in the erlotinib group (median 7.9 vs 6.8 months, p=0.0077)
AEs
<ul style="list-style-type: none"> AE profiles were similar in each group. Grade ≥3 AEs were comparable in both groups (224 [57%] afatinib vs 227 [57%] erlotinib). There were higher incidences of treatment-related Grade 3 diarrhoea with afatinib (10% vs 2%) and Grade 3 stomatitis with afatinib (4% vs 0%), while Grade 3 rash or acne was higher with erlotinib (6% vs 10%)

AE, adverse event; DCR, disease control rate; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.



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4. DATA OVERVIEW: THE LUX-HEAD AND NECK CLINICAL TRIAL PROGRAMME

Afatinib is being investigated in head and neck squamous cell cancer (HNSqCC) in the [LUX-Head and Neck](#) clinical trial programme.

Results from LUX-Head and Neck 1 showed that afatinib is the first tyrosine kinase inhibitor to significantly delay tumour growth vs chemotherapy in patients with recurrent and/or metastatic HNSqCC following failure of their previous platinum-based therapy.²¹

Patients taking afatinib experienced a significant delay in tumour growth of 2.6 vs 1.7 months with chemotherapy, which translated into a 20% reduction in risk of disease progression.²¹

LUX-Head and Neck 1 ²¹ (afatinib vs methotrexate)
PFS (primary endpoint)
<ul style="list-style-type: none">2.6 vs 1.7 months (statistically significant, p=0.030)
Tumour shrinkage (secondary endpoint)
<ul style="list-style-type: none">Tumour shrinkage was observed in 35.0% of patients in the afatinib arm compared with 22.0% of patients in the chemotherapy arm
ORR (secondary endpoint)
<ul style="list-style-type: none">10.0% vs 6.0% (p=0.10)
DCR (secondary endpoint)
<ul style="list-style-type: none">49.0% vs 39.0% (statistically significant, p=0.035)
HRQoL (secondary endpoint)
<ul style="list-style-type: none">In HRQoL questionnaires, patients taking afatinib had less pain, particularly jaw pain, over time (p=0.03). There were no significant differences over time in global health status (p=0.78) or swallowing (p=0.98)
OS (secondary endpoint)
<ul style="list-style-type: none">No significant difference between afatinib and chemotherapy was observed (median 6.8 vs 6.0 months)
AEs
<ul style="list-style-type: none">The most frequent drug-related AEs (Grade ≥3) were rash/acne (10.0%) and diarrhoea (9.0%) with afatinib, and stomatitis (8.1%) and neutropenia (6.0%) with chemotherapy. Drug-related AEs led to dose reductions in 32% patients in the afatinib group vs 42% of patients in the chemotherapy group. Drug discontinuations occurred in fewer patients receiving afatinib vs chemotherapy (7% vs 16%)

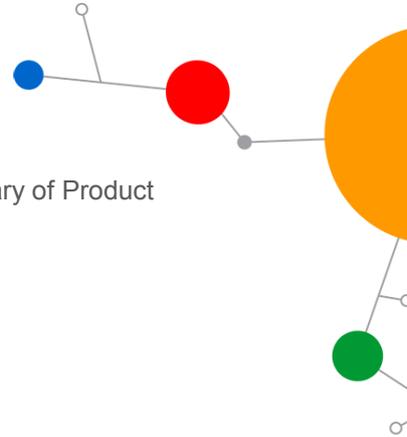
AE, adverse event; DCR, disease control rate; HRQoL, health-related quality of life; OS, overall survival; ORR, objective response rate; PFS, progression-free survival.

5. TOLERABILITY

The side effects of afatinib are predictable, generally manageable and reversible. In studies to date, drug-related adverse events (AEs) were largely related to the gastrointestinal tract (diarrhoea) and skin disorders (rash), which is in line with EGFR tyrosine kinase inhibition.⁶⁻²⁷ For further details, please refer to the AEs section in each of the above studies (LUX-Lung 3, 6, 7, 8 and LUX-Head and Neck 1) and the Summary of Product Characteristics.¹

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More information on the dosing of afatinib can be found [here](#) and also in the Summary of Product Characteristics.¹



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ONCOLOGY FROM BOEHRINGER INGELHEIM

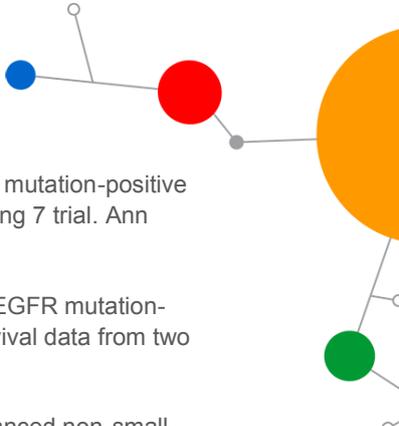


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Abbreviated EU SmPC:

EGFR M+ NSCLC and sqNSCLC

GIOTRIF®: Irreversible ErbB family blocker. **Active substance:** Afatinib. **Indications:** GIOTRIF is indicated as monotherapy for (1) patients with locally advanced or metastatic NSCLC with activating EGFR mutations not previously treated with EGFR TKIs, (2) patients with NSCLC of squamous histology progressing on or after platinum-based chemotherapy. **Posology:** The recommended dose is 40 mg once daily, orally. Not recommended in patients with an eGFR <15ml/min and severe hepatic impairment. **Contraindications:** Hypersensitivity to afatinib or any of the excipients. **Interactions:** Potent P-gp inhibitors may lead to increased afatinib exposure, concomitant treatment with potent P-gp inducers may lead to a reduction in afatinib exposure. Afatinib is not an inhibitor or inducer of CYP enzymes. **Undesirable effects:** Paronychia, cystitis, decreased appetite, dehydration, hypokalaemia, dysgeusia, conjunctivitis, dry eye, epistaxis, rhinorrhoea, diarrhoea, stomatitis, nausea, vomiting, cheilitis, dyspepsia, alanine aminotransferase increased, aspartate aminotransferase increased, rash, acneiform dermatitis, pruritus, dry skin, palmar-plantar erythrodysesthesia syndrome, nail disorders, Stevens-Johnson syndrome, toxic epidermal necrolysis, muscle spasms, renal impairment/renal failure, pyrexia, weight decreased, interstitial lung disease, keratitis, pancreatitis. **Presentations:** 20 mg, 30 mg, 40 mg, and 50 mg film-coated tablets. For detailed information, please refer to the published Prescribing Information.

Supply classification: POM.



This medicine is subject to additional monitoring.

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EGFR M+, epidermal growth factor receptor mutation positive; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

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