14th January 2016

Tarceva® (erlotinib): First line maintenance indication now restricted to treatment of patients whose tumors harbor an EGFR-activating mutation

Dear Healthcare Provider,

F. Hoffmann-La Roche Ltd. would like to inform you about an important change to the Tarceva® (erlotinib) prescribing information.

Summary

- **Tarceva is no longer indicated for the first line maintenance treatment in patients without an epidermal growth factor receptor (EGFR) activating mutation based on data from the IUNO study. This study led to the conclusion that the benefit-risk of Tarceva for maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after 4 cycles of standard platinum-based first-line chemotherapy whose tumors do not harbor an EGFR-activating mutation is no longer considered favorable.**

- **The indication has been revised to the following: *"Tarceva is also indicated for switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy"*.**

- **This information is being sent in agreement with the European Medicines Agency.**

Further information

The IUNO study is a randomized, double-blind, placebo-controlled, phase 3 study of first-line maintenance Tarceva versus initiating Tarceva at the time of disease progression in patients with advanced NSCLC whose tumor did not harbor an EGFR-activating mutation (exon 19 deletion or exon 21 L858R mutation) and who had not progressed following 4 cycles of platinum-based chemotherapy. Patients were randomized to receive maintenance Tarceva or maintenance placebo followed by chemotherapy/best supportive care or Tarceva upon disease progression, respectively.

Overall survival (OS) was not superior in patients randomized to receive maintenance Tarceva followed by chemotherapy upon progression compared to patients randomized to receive maintenance placebo followed by Tarceva upon progression (HR=1.02, 95% CI, 0.85 to 1.22, p=0.82). In the maintenance phase, patients who received Tarceva also did not have superior

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progression-free survival (PFS) compared with patients who received placebo (HR=0.94, 95% CI, 0.80 to 1.11, p=0.48).

Based on the results observed in the IUNO study, Tarceva is no longer indicated for maintenance treatment in patients without an EGFR activating mutation. Consequently, the first line maintenance indication in section 4.1 Therapeutic indication – Non small cell lung cancer of the Summary of Product Characteristics has been revised as indicated in the summary section above.

Changed from:

> "*Tarceva is also indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of standard platinum-based first-line chemotherapy*"

Changed to:

> *"Tarceva is also indicated for **switch** maintenance treatment in patients with locally advanced or metastatic NSCLC **with EGFR activating mutations and** stable disease **after first-line chemotherapy***"

The product information for Tarceva has been updated to implement this change (see Annex).

Call for Reporting

Healthcare professionals should report any suspected side effects of Tarceva to national reporting requirements.

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme. Please report

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.
- All suspected ADRs associated with new drugs and vaccines identified by the black triangle ▼

It is easiest and quickest to report ADRs online via the Yellow Cards website - https://yellowcard.mhra.gov.uk/.

Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gsi.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- or by downloading and printing a form

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

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Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554.

Company contact point
For further information or any questions please contact Roche Medical Information by phone on +44(0)800 328 1629 or via e-mail medinfo.uk@roche.com

Yours faithfully,

Dr Daniel Thurley MA MB BChir MRCP FFPM
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Annex

Revised labelling: Only the paragraphs from the Tarceva Summary of Product Characteristics that have been updated are included here. Changes are in bold and underlined.

Refer to the full Summary of Product Characteristics for comprehensive information to support the use of the product.

4.1 Therapeutic indications

Non-Small Cell Lung Cancer (NSCLC):
Tarceva is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations.

Tarceva is also indicated for switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy.

Tarceva is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

When prescribing Tarceva, factors associated with prolonged survival should be taken into account.

No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with Epidermal Growth Factor Receptor (EGFR)-IHC negative tumours (see section 5.1).

4.8 Undesirable effects

In **two** other double-blind, randomized, placebo-controlled Phase III **studies** BO18192 (SATURN) **and BO25460 (IUNO**); Tarceva was administered as maintenance after first-line chemotherapy. **These studies were conducted in a total of 1532 patients** with advanced, recurrent or metastatic NSCLC following first-line standard platinum-based chemotherapy, no new safety signals were identified.

The most frequent ADRs seen in patients treated with Tarceva in **studies** BO18192 **and BO25460** were rash and diarrhoea (**see Table 2**). No Grade 4 rash or diarrhoea was observed **in either study**. Rash and diarrhoea resulted in discontinuation of Tarceva in 1% and <1% of patients, respectively, **in study BO18192, while no patients discontinued for rash or diarrhoea in BO25460.** Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 8.3% and 3% of patients, respectively, **in study BO18192 and 5.6% and 2.8% of patients, respectively, in study BO25460.**

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Table 2: Most frequent ADRs in Studies BO18192 (SATURN) and BO25460 (IUNO)

	BO18192 (SATURN)*		BO25460 (IUNO)*	
	Tarceva n=433	Placebo n=445	Tarceva n=322	Placebo n=319
	%	%	%	%
Rash, all grades	49.2	5.8	39.4	10.0
Grade 3	6.0	0	5.0	1.6
Diarrhoea, all grades	20.3	4.5	24.2	4.4
Grade 3	1.8	0	2.5	0.3

***Safety analysis population**

Other Observations:
Safety evaluation of Tarceva is based on the data from more than **1500** patients treated with at least one 150 mg dose of Tarceva monotherapy and more than 300 patients who received Tarceva 100 or 150 mg in combination with gemcitabine.

5.1 Pharmacodynamic properties

-Maintenance NSCLC therapy after first-line chemotherapy (Tarceva administered as monotherapy):

The efficacy and safety of Tarceva as maintenance after first-line chemotherapy for NSCLC was **investigated** in a randomized, double-blind, placebo-controlled trial (BO18192, SATURN). This study was conducted in 889 patients with locally advanced or metastatic NSCLC who did not progress after 4 cycles of platinum-based doublet chemotherapy. Patients were randomized 1:1 to receive Tarceva 150 mg or placebo orally once daily until disease progression. The primary endpoint of the study **included** progression free survival (PFS) in all patients**.** Baseline demographic and disease characteristics were well balanced between the two treatment arms. Patients with ECOG PS>1, significant hepatic or renal co-morbidities were not included in the study.

In this study, the overall population showed a benefit for the primary PFS end-point (HR= 0.71 p< 0.0001) and the secondary OS end-point (HR= 0.81 p=0.0088). However the largest benefit was observed in a predefined exploratory analysis in patients with EGFR activating mutations (n= 49) demonstrating a substantial PFS benefit (HR=0.10, 95% CI, 0.04 to 0.25; p<0.0001) and an overall survival HR of 0.83 (95% CI, 0.34 to 2.02). 67% of placebo patients in the EGFR mutation positive subgroup received second or further line treatment with EGFR-TKIs.

The BO25460 (IUNO) study was conducted in 643 patients with advanced NSCLC whose tumors did not harbor an EGFR-activating mutation (exon 19 deletion or exon 21 L858R mutation) and who had not experienced disease progression after four cycles of platinum-based chemotherapy.

The objective of the study was to compare the overall survival of first line maintenance therapy with erlotinib versus erlotinib administered at the time of disease progression. The study did not meet its primary endpoint. OS of Tarceva in first line maintenance was not superior to Tarceva as second line treatment in patients whose tumor did not harbor an EGFR-activating mutation (HR= 1.02, 95% CI, 0.85 to 1.22, p=0.82). The secondary endpoint of PFS showed no difference between Tarceva and placebo in maintenance treatment (HR=0.94, 95 % CI, 0.80 to 1.11; p=0.48).

Based on the data from the BO25460 (IUNO) study, Tarceva use is not recommended for first-line maintenance treatment in patients without an EGFR activating mutation.

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