

## BIBW 2992 (TOVOK™)

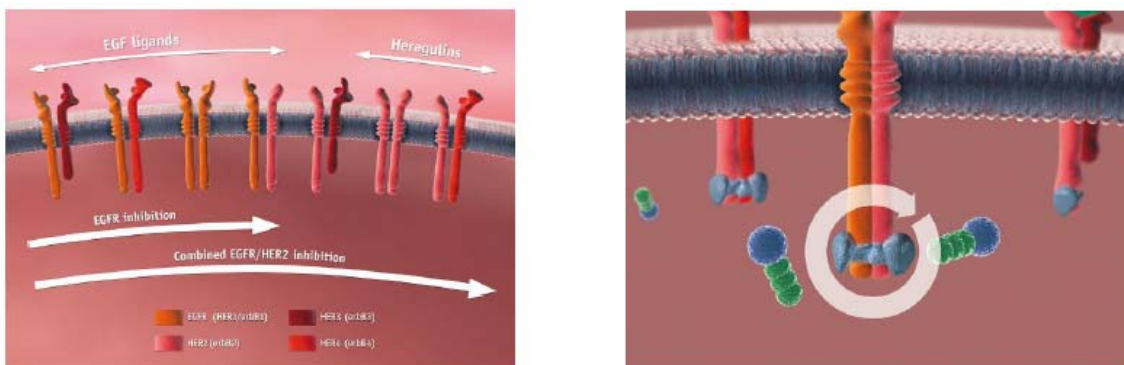
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### 1. Overview

BIBW 2992 (Tovok™)\* is a novel representative of the new generation of tyrosine kinase inhibitors. This new compound is a potent and irreversible inhibitor of both the EGFR and HER2 kinases. Both of these are involved in cell proliferation, differentiation and apoptosis (programmed cell death) and inhibition may play a critical role in the prevention of tumour growth and spread. BIBW 2992 (Tovok™) irreversibly binds to the receptors and inhibits the down stream signalling cascade, which in turn may inhibit cell growth and induce cell death (apoptosis) in cancer cells.

BIBW 2992 (Tovok™) is being investigated for various indications, including non-small cell lung cancer (NSCLC), breast cancer, colorectal cancer and head and neck cancer.<sup>1,2</sup> BIBW 2992 (Tovok™) is currently in phase IIb/III clinical development in NSCLC.

The irreversible nature of BIBW 2992 (Tovok™) and its potent and selective dual inhibition of EGFR and HER2 provides the potential benefits of improved inhibition of tumour cell proliferation and efficacy across a broad range of indications compared to single, reversible, receptor blocking.<sup>3</sup>

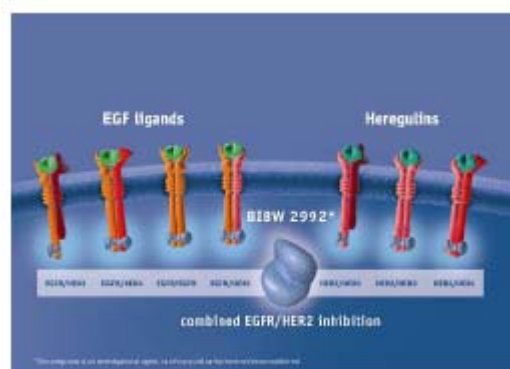


### 2. Mechanism of action

Cell proliferation, differentiation and programmed cell death (apoptosis) are tightly regulated in healthy tissues by a variety of external signals working via receptors that activate intracellular signal transduction pathways. Cancer cells often acquire genetic mutations that deregulate these pathways, resulting in malignant cells that proliferate uncontrollably and do not respond to the signals that normally activate apoptosis. Epidermal Growth Factor Receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) are two receptors involved in the signalling pathways and can be disrupted by cancer cells, causing over activity and further genetic instability which results in subsequent generations of cells displaying unusual traits. Over-expression of EGFR and HER2 is associated with poor prognosis and advanced-stage cancers.<sup>4</sup>

\* BIBW 2992 (Tovok™) is an investigational compound. Its safety and efficacy have not yet been fully established.

Signal transduction inhibitors work by blocking the key pathways involved in cell growth and division which in turn prevent activation of the receptors which, as a consequence, interferes with normal cell processes. Inhibition of one receptor type alone may not be sufficient for optimal inhibition of tumour cell proliferation and survival.<sup>3</sup> BIBW 2992 (Tovok™), as a selective and potent dual inhibitor of EGFR and HER2 receptor tyrosine kinases, broadens its reach in terms of its efficacy and potential indications. In addition, due to the irreversible binding, BIBW 2992 (Tovok™) is active against receptors that are resistant to first-generation inhibitors.<sup>5</sup>



### 3. Development Status

BIBW 2992 (Tovok™) is currently in Phase IIB/III clinical development in NSCLC, the most common type of lung cancer. Known as LUX-Lung 1, this is a randomised, double-blind study of BIBW 2992 (Tovok™) plus best supportive care (BSC) versus placebo plus BSC in NSCLC patients who have failed first-generation EGFR TKIs erlotinib or gefitinib.

As EGFR and HER2 play a pivotal role in many solid tumours, BIBW 2992 (Tovok™) is also being investigated in various indications including NSCLC, breast, colorectal and head and neck cancers.

### 4. Data Overview

#### *Efficacy and Safety*

- BIBW 2992 (Tovok™) has shown a stable disease rate of approximately 40% in phase I studies in various tumour types.<sup>6</sup>
- Tovok™ BIBW 2992 has been shown to be active in patients with advanced NSCLC including those with brain metastasis.<sup>7</sup>
- New data presented from the ongoing phase II clinical study (LUX-Lung 2) showed lung cancer patients with activating epidermal growth factor receptor (EGFR) mutations treated with BIBW 2992 experienced a high overall response rate – one in two patients (64%; 43/67 patients) had a partial response – and a high rate of disease control (96%; 64/67 patients).
- BIBW 2992 (Tovok™) has activity in NSCLC with activating mutations which show no or low response to gefitinib or erlotinib.<sup>5</sup>
- BIBW 2992 (Tovok™) demonstrated superior activity to gefitinib and trastuzumab in SKOV-3 ovarian cancer and NCI-N87 gastric cancer models respectively.<sup>1</sup>

#### *Tolerability*

Generally BIBW 2992 (Tovok™) is well tolerated. To date, 800 patients have been treated with BIBW 2992 (Tovok™) through enrolment in phase I and II clinical studies.<sup>8-13</sup>

Interim safety data recently presented from the LUX-Lung phase III trial programme also showed encouraging results, demonstrating BIBW 2992 (Tovok™) to be well tolerated. The most common drug related adverse events were diarrhoea and skin disorders.

## 5. Clinical potential

Signal transduction inhibitors are a key development target in cancer research. The dual inhibition and irreversible binding properties of BIBW 2992 (Tovok™) may provide benefits over other compounds targeting the EGFR and HER2 pathways.

At this stage in its development, results have indicated that BIBW 2992 (Tovok™) may have potential benefits compared to other signal transduction inhibitors, with a comparable tolerability profile. The ongoing study programme evaluating BIBW 2992 (Tovok™) in a number of indications will provide more clinical data to further establish the benefits of this compound demonstrated in earlier studies.

## References

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