Paul Bloomfield
Medical Director

Uptravi▼(selexipag): concomitant use with strong CYP2C8 inhibitors (e.g. gemfibrozil) now contraindicated

Dear healthcare professional,

Actelion, in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA), would like to inform you of the following important information:

Summary

- **A contraindication has been introduced for concomitant use of Uptravi (selexipag) with strong CYP2C8 inhibitors (e.g. gemfibrozil).**
- **Concomitant administration of selexipag with gemfibrozil results in an 11-fold increase in exposure to the active metabolite of selexipag, increasing the risk of selexipag adverse effects.**
- **Adjustment of dose of selexipag should be considered in cases where a moderate CYP2C8 inhibitor (e.g. clopidogrel, deferasirox and teriflunomide) is co-administered or discontinued.**

Background on the safety concern
Uptravi, which contains the active substance selexipag, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III.

Selexipag and its active metabolite ACT-333679 are prostacyclin (IP) receptor agonists. The active metabolite is the main contributor to the efficacy of selexipag. Stimulation of the IP receptor by selexipag and its active metabolite leads to vasodilatory as well as anti-proliferative and anti-fibrotic effects.

The pharmacokinetics of selexipag and its active metabolite was investigated in healthy male subjects in the presence of gemfibrozil, a strong CYP2C8 inhibitor. Exposure to selexipag increased approximately 2-fold whereas exposure to the active metabolite increased approximately 11-fold.

The number and intensity of prostacyclin-associated adverse events reported after concomitant administration of selexipag and gemfibrozil were higher (20/20 [100%] of subjects), compared to selexipag administered alone (15/20 [75%] of subjects). This is consistent with the 11-fold increase in exposure to the active metabolite, the major contributor to the pharmacodynamic effects of selexipag.

An 11-fold increase in the exposure to the active metabolite in the presence of the strong CYP2C8 inhibitor is likely to result in significant patient discomfort and side effects which may lead to treatment

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discontinuation. Therefore, a contraindication for the concomitant use of selexipag and strong CYP2C8 inhibitors (e.g. gemfibrozil) has been introduced.

The effect of moderate inhibitors of CYP2C8 (e.g. clopidogrel, deferasirox, teriflunomide) on the exposure to selexipag and its active metabolite has not been studied. An adjustment of the dose of selexipag should be considered in cases where a moderate inhibitor of CYP2C8 is co-administered or discontinued.

The product information for selexipag will be updated accordingly.

Call for reporting
Healthcare professionals are reminded to report any suspected adverse reactions via the national spontaneous reporting system via the MHRA, 151 Buckingham Palace Rd, Belgravia, London SW1W 9SZ or via www.mhra.gov.uk/yellowcard Email info@mhra.gov.uk Telephone 020 3080 6000 Fax 020 3118 9803

Adverse events should also be reported to Actelion Pharmaceuticals UK Ltd on +44 (0)208 987 3333 or drugsafetyuk@actelion.com

Uptravi is a medicinal product subject to additional monitoring as it was only recently introduced to the market. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Yours sincerely

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