The compound has been originally disclosed in EP 0364417 B1[75] belonging to Kabi-Pharmacia. The drug was launched in 1996 in the U.S. and in Europe[76]. The patent protection for the basic compound expired in March 2011.

During previous research at Columbia University[77] it had been found that prostaglandine $PGF_{2\alpha}$ and its iso-propyl ester could lower the intraocular pressure in patients with open-angle glaucoma. However, these compounds had low therapeutic value due to the poor cornea permeability and their side effects (e.g. ocular irritation, conjunctival hyperemia). Further studies at Kabi Pharmacia addressed these issues. Variation in the structure of $PGF_{2\alpha}$ allowed achieving the desired effects. Furthermore, a more efficacious compound was obtained by separating the 15*R*-epimer (Formula 3). The ester prodrug is hydrolyzed on the cornea and the parent acid is active as a selective prostaglandin F-receptor agonist and reduces the intraocular pressure preventing further optic nerve damage and preserving remaining vision.[78]

2. Patent Portfolio

a) Process

The initial method of synthesis covered by the basic patent family (EP 0569046 resp. WO 90/02553) was based on the final separation of the two epimers at C15 (Formula 3) resulting therefore in a tedious procedure and in low yield taking in account the fact that only the 15*R*-epimer is desired. Further studies were therefore directed to solve the

75 Filed in September 1989 and invoking a Swedish application priority: SE 8803110 and SE 8803855.

76 E.g. Marketing Authorisation in Sweden 18 July 1996: see European Patent Register, Legal status: EP 0364417, https://register.epo.org/espacenet/application?number=EP89850294&lng=en&tab=legal, (last visited Aug. 3, 2012).

77 U.S. 4,599,353.

78 Information about Xalatan were taken from Sajiv K. Nair, Kevin E. Henegar, Modern Drug Synthesis 329-330 (Jie Jack Li, Douglas S. Johnson eds., 1st ed. 2010).

issues to obtain latanoprost in good yield, large amount and desired purity. The patent family EP 0544899 claims the process for the preparation of the 15*R*-epimer (latanoprost), based on a selective reduction of a key intermediate[79] and the various intermediates of the synthesis. This patent expired in June 2012. An earlier patent family EP 0495069 was also directed to solve the same issue. However, it covers only an advanced intermediate and the selective reduction is more tedious being based on the use of protecting groups.[80] The last patent of the originator company (US 6,689,901, filed in June 2002) covers instead the selective preparation of the other (15*S*) epimer. This could be the result of a failed process strategy.

b) Formulation

It appears that no particular research interest had been directed to the identification of specific formulations with improved characteristics. As the standard therapy using latanoprost involves a topical application directly to the target organ (eye), seemingly no particular difficulties needed to be overcome. Only one patent has been obtained by Pfizer with respect to a different dosage form, EP 1471890 B1. This patent claims an intraoral dosage in form of a disintegrating tablet with the effect that the drug is taken up via the oral mucosa of the treated subject. It must be noted however, that this patent is neither directed specifically to latanoprost, nor does this appear to the skilled artisan the most straightforward way of administering the drug, which has to act on the eye.

79 EP 0544899 B1 claims 1 and 2: reduction of the α,β-unsaturated enone key intermediate.

80 EP 0495069 B1: claim 1.

c) Combination Therapy

The earliest claimed combination therapy of latanoprost is the one which combines the drug with a tyrosinase inhibitor as claimed in EP 0977575 B1. The specific reason behind this combination is the avoidance of a known side effect of latanoprost which very often leads to an increased pigmentation of the eye.[81]

One of the more important patent applications in this field appears to have been WO 02/38158 A1. This application dealt with a combination of timolol and latanoprost, which is the basis for a marketed composition named Xalacom®. During the European proceedings however, Pharmacia had not been able to establish novelty over a published experimental clinical report[82] and the application finally was abandoned.[83]

Further combinations for which patent applications had been filed or for which patents have been granted are those with other drugs known in the field of glaucoma treatment.

As such, a series of applications has been directed to combining latanoprost with inhibitors of Cyclooxygenase-2. WO 02/05815 claims a combination of the blockbuster celecoxib (trade name Celebrex®) with latanoprost. The application entered the European phase and later was withdrawn.[84] WO 2005/021004 makes the same claim but did not enter the regional phases. WO 2005/099691 again claims and exemplifies the combination, but results withdrawn after entry into the European phase.

A claimed combination of latanoprost with Pfizer's antihypertensive (diuretic) eplerenone (trade name Inspra®) resulted in the grant of US 7,015,210.

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81 See EP 0977575 B1, description lines 8-22.

82 M. Diestelhorst, Brigitta Almegård, *Comparison of two fixed combinations of latanoprost and timolol in open-angle glaucoma*, 236 Graefe's Archive for Clinical and Experimental Ophthalmology 577, (1998).

83 EPO register.

84 *Id*.

Pfizer's ongoing research on glaucoma led to the discovery of new active compounds. Some patents covering such compounds also include claims to combinations with Xalatan.[85] Further patent applications were directed to combinations involving carbonic anhydrase inhibitors which are also used as treatments for glaucoma and ocular hypertension. None of these[86] however, progressed to a granted patent as they all result to be withdrawn in the European phase.

d) New Uses

With respect to new uses identified by the originator it appears that no substantial amount of research had been dedicated to it. The only application in this field is WO 95/11003 which is directed to a method of using latanoprost and its analogues for increasing the pigmentation of tissues and especially hair. However, this is not the fruit of dedicated studies into identifying further purposes for the compound at hand, but a known side-effect of the drug.[87, 88] Though the application entered the European phase, it results as withdrawn as novelty was objected.[89]

e) Delivery Devices

Two applications were directed to methods of treatment using a special applicator for the drug latanoprost.[90] The applicator is in form of an aerosol discharger and dispenses an effective amount of the drug directly to the eye. While certainly giving the product a competitive

85 E.g. WO 2006/048750 A2, EP 1893609 B1, WO 2006/134481 A1.
86 WO 2004/014352, WO 2008/075155.
87 Upon the topical use in the eye, the eyelids darken as well as does the iris colour due to increase in pigmentation.
88 M.A. Johnstone, *Hypertrichosis and increased pigmentation of eyelashes and adjacent hair in the region of the ipsilateral eyelids of patients treated with unilateral topical latanoprost*, 124 Am. J. Ophthalmol. 544, (1997).
89 See procedural documents available via EPO register.
90 Published as WO 2004/028420 A1 and WO 2004/028421 A1.

edge with respect to ease of application, this method of administering the drug to the eye would not have created any market entry barrier as there is a sufficient number of generic ways to do so. In any case, these applications have not been pursued and are deemed withdrawn.[91]

f) Packaged Product

In 2005, Pharmacia & Upjohn filed two patent applications[92] in the United States exclusively which are directed to a special method of packaging latanoprost into plastic vials, as well as to the plastic vials filled with the drug *per se*. It appears, that there existed a need to stabilise the packaged drug and that the company had identified a solution for this. However, both applications were objected to by the USPTO under the aspect of unity of invention[93] and the company by that time must have had decided not to pursue the issue any further, as both patent applications result abandoned by mid-2008.

A further patent application has been filed with respect to the packaging of a combination of the drugs timolol and latanoprost, which is sold under the trade name Xalacom.[94] Also this application has been refused due to lack of unity and was then abandoned.[95]

3. Use of Procedural Provisions

a) Divisional of Basic Patent

The basic patent EP 0364417 B1 gave rise to 9 divisional applications filed between 1993 and 2003 which are directed to more specific embodiments comprised in the parent application. In particular, EP

91 *Supra* note 89.
92 Published as US 2005/0049311 A1 and US 2005/0287325 A1.
93 See USPTO *supra* note 68.
94 Published as US 2005/0048122 A1.
95 See USPTO *supra* note 68.