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All in a Day's Work

Putting the pressure on glaucoma with 24/7 IOP control.

Highlights from the "Decoding Glaucoma: A place for 24-hour IOP control" educational symposium organized and funded by Santen and held at the 13th EGS Congress, Florence, Italy, on May 19, 2018. The symposium was moderated by Carlo Traverso (University of Genova, Italy), and featured presentations and comments from Luciano Quaranta (University of Brescia, Italy), Antonio Figueiredo (University of Lisbon, Portugal), and Anastasios Konstas (Aristotle University of Thessaloniki, Greece).

PP-MIGS-EMEA-0017 – Date of preparation October 2018

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The standard of care for glaucoma has changed radically over the years – but the ultimate outcomes have changed little. As Dr. Antonio Figueiredo says: "Glaucoma has been a leading cause of blindness for a century – yet, today, the risk of bilateral blindness within 15 years of diagnosis is 16 percent. We must be doing something wrong!"

The sense that we are missing something is clear. But, at present, ocular hypertension (OHT) appears to be the major risk factor for glaucoma – not only that, it is the one risk factor we can treat. Investigations that provide evidence for IOP control as a means of inhibiting disease progression include: the Early Manifest Glaucoma Trial (EMGT); Advanced Glaucoma Intervention Study (AGIS); Collaborative Initial Glaucoma Treatment Study (CIGTS); and the Collaborative Normal Tension Glaucoma Study (CNTGS).

Nevertheless, we have yet to address several important issues relating to IOP control, measurement and monitoring. Are a few readings a year really adequate? If not, how many do we need? At what times of day? Remember, IOP is not a steady state – it exhibits short- and long-term fluctuations, minimum pressures, peak pressures... Which of these should we focus on? Are all treatments equivalent regarding their ability to control IOP over 24 hours? Thus, the question of how to best monitor and control IOP in the context of real-world clinical practice remains a vexing one: this symposium provides some answers.

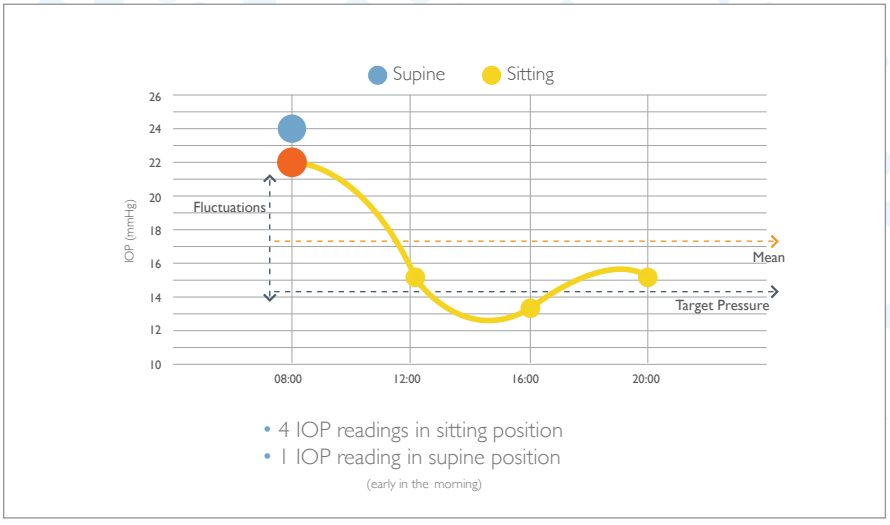

Figure 1. Diurnal phasing of IOP. IOP exhibits day-time fluctuations; the early-morning supine reading is higher than the equivalent sitting reading.

The rhythm of glaucoma

It is clear that IOP fluctuates both during the day (Figure 1) and over periods of years (Figure 2). Measuring IOP over 24-hour periods reveals a circadian rhythm (Figure 3) that likely reflects modulations in the inflow-outflow balance, which is, in turn, related to several variables, including postural changes (non-supine to supine at night); geographical changes; autoregulatory mechanisms; decreased nocturnal aqueous humor flow and production; and decreased nocturnal outflow (both pathways). "We should take these variables into account when measuring and managing IOP," says Prof. Luciano Quaranta.

Dr. Figueiredo concurs: "Glaucoma is significantly affected by nocturnal changes, not least the postural change – remember, we spend about a third of our lives in the supine position!" There are significant differences between sitting and supine IOP at all time points, he adds, but most particularly in the early morning. "In 24-hour studies, peak IOP is on average 5 mmHg higher than office-hour peaks. Peak IOP values occur outside normal office hours in 52 percent of patients, often during sleep." Even in apparently controlled patients, many of the highest IOP readings occur outside normal office hours (Figure 4). One study (2) showed that a nocturnal peak occurs in 67.7 percent of patients, and a diurnal peak in only 12.9 percent.

Two main bodies of work exist relating to 24-hour IOP (Figure 5). American investigators report that IOP rises nocturnally, with glaucoma patients tending to show peak pressures at about 4–5 am. European investigators, by contrast, report that intraocular pressure tends to peak around 10 am in untreated glaucomatous patients. Why the difference? Prof. believes it is a consequence of different methodology. "European investigators relied on the gold standard of Goldmann applanation tonometry (GAT); US workers used mainly pneumotonometer applanation tonometry."

Do these IOP rhythms have implications for glaucoma management? Dr. Figueiredo is clear: "We need to change the way we evaluate IOP: instead of taking random 'snapshot' measurements of IOP three or four times each year, we should assess the entire 24-hour profile of an individual's IOP and tailor our target pressure and medication strategy to that profile." This point is particularly important, he adds, where disease is progressing despite apparent control of IOP. Prof. Konstas' views on the matter are equally concrete: "Relying on a single pressure measurement is like relying on a single photograph to guess the plot of a film – yet we frequently make clinical decisions on this basis!" This limitation, says Prof. Konstas compromises every step of our care.

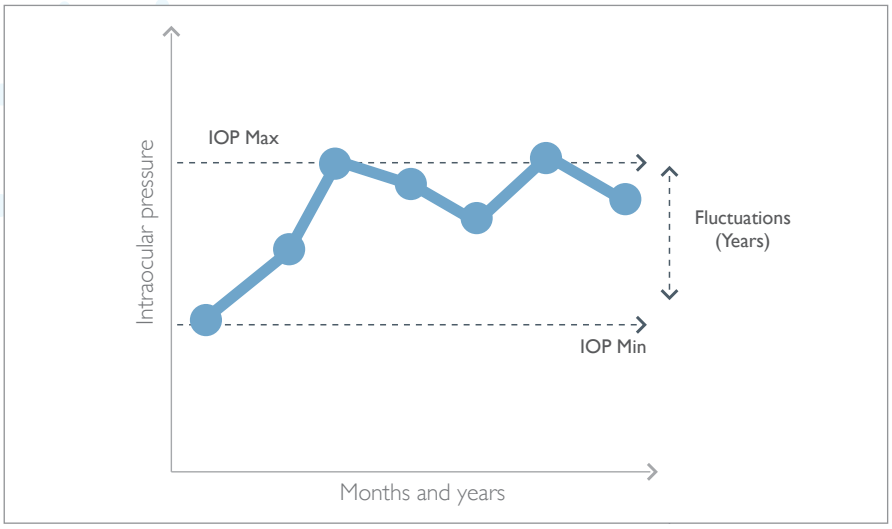

Figure 2. IOP fluctuates over time.

Figure 3. IOP circadian rhythm. In both supine (blue data points) and sitting positions (red data points), IOP troughs appear at the end of the diurnal period, whereas peaks appear at the end of the nocturnal period (1).

Taking measurements that are representative of the IOP profile

Without 24-hour monitoring, it may be difficult to understand why some patients progress. But how do we obtain 24-hour IOP data that is comprehensive enough to guide clinical practice? Prof. Quaranta suggests two main options for sampling IOP: diurnal phasing or 24-hour phasing.

Option 1: diurnal phasing

"In our glaucoma clinic of 3,400 patients per year, we perform phased measurements on perhaps 340 individuals – typically those with good concordance between visual field data and optic nerve head appearance," says Prof. Quaranta. For such patients, he recommends four IOP measurements during the day in a sitting position (Figure 1). "And if you want to estimate likely night-time IOPs without taking measurements outside office hours, taking the early-morning reading in the supine position is a reasonable surrogate for the nocturnal situation." The early-morning time point, he adds, may have the benefit of being in a medication trough if the reading is taken before a patient's morning dose; this gives clinicians a better idea of actual pressure fluctuations.

Furthermore, given that there is fair to good agreement for IOP at any given time on different days, a 'long-term' diurnal phasing of IOP measurement may be a valid choice for identification of fluctuations over longer timescales. To highlight the importance of this point, Prof. Quaranta describes a case in which IOP fluctuations over a five year period were associated with glaucoma progression.

Option 2: 24-hour phasing

Obtaining IOP measurements outside office hours – let alone in the middle of the night – is challenging. Prof. Quaranta cites a study (3) indicating that the collection of both supine and sitting IOPs may enable identification of 24-hour IOP characteristics and thus limit the need for obtaining 24-hour curves to a minority of patients (Figure 6). "Clinicians should particularly consider this approach for very complex patients who exhibit disease progression despite apparently normalized IOP," says Prof. Quaranta.

Technological advances may enable IOP measurement outside office hours: one example is Triggerfish (Sensimed AG, Lausanne, Switzerland), a soft contact lens with embedded strain gauges. Changes in diameter correspond to changes in IOP, and are read by a microprocessor and transmitted to a recorder unit. The device takes 60 seconds of continuous measurements every ten minutes for 24 hours. Unfortunately, not all patients tolerate the Triggerfish contact lens, and the values it provides are in arbitrary units,

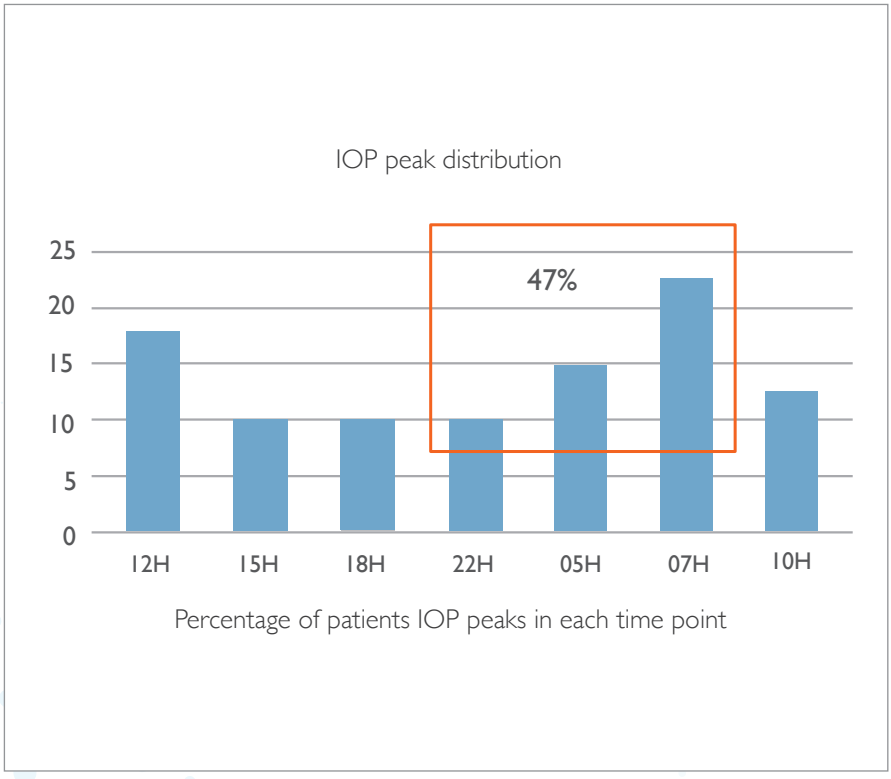

Figure 4. IOP peak distribution.

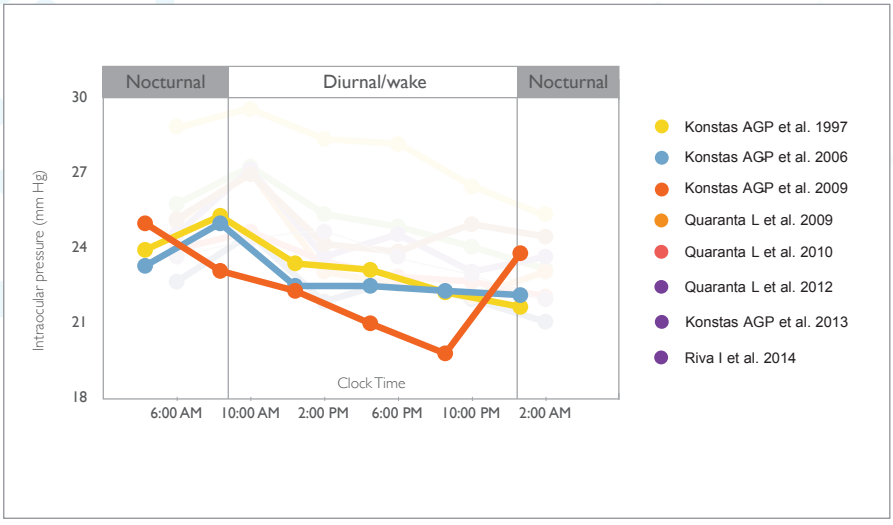

Figure 5. Comparison of data on 24-hour IOP. European data suggest that IOP peaks around 10 am; US studies indicate a 4–5 am peak.

without any established correlation to IOP values (4). "Sophisticated, but expensive and not very user-friendly," summarizes Dr. Figueiredo.

What if the patient could self-monitor IOP outside office hours? The Icare Home device uses 'rebound technology' – a small probe briefly contacts the cornea and records deceleration and contact time, which change as a function of IOP. Advantages include comfort and the availability of a positioning system, which assists in correct alignment of the device.

Dr. Figueiredo has been applying the Icare Home self-monitoring system for a year (see Case Studies – Box 1). "Icare is not easy – especially for older patients. It is associated with a minimum 30 minute learning curve, and occasional loss of measurements." In terms of reliability, Dr. Figueiredo cites a systematic review, showing that more than 50 percent of Icare measurements were within 2 mmHg of Goldmann values, and 75 percent of Icare and Goldmann values were within 3 mmHg of each other. Adds Dr. Figueiredo, "Our own experience with this device is that 57 percent of patients are within 2 mmHg of Goldmann, and 70 percent of them are within 3 mmHg." What kind of data does it generate? "We find that almost all patients have IOP peaks that fall outside normal office times," says Dr. Figueiredo. "And over 70 percent of all peaks occurred outside office times!" For clarification, he adds, "Not all these peaks are clinically significant, but 10 percent were over 22 mmHg – and remember that these are patients whose IOP was apparently controlled." Clearly, Icare-type data may significantly alter patient management in the real world (Box 1).

Identifying the target

Evidently, 24-hour IOP readings are important – but we also need to know what specific IOP values should be used to guide decisions and treatment strategies. Is there a magic number? Perhaps: a five-year retrospective 24-hour monitoring study of peak IOP and glaucomatous progression in primary open angle glaucoma (POAG) patients (5) indicates that around 75 percent of patients with peak daytime or 24-hour IOP of 18 mmHg or below remained stable (Figure 7).

Similarly, the AGIS study – looking at the role of long-term fluctuations in disease progression – reported little or no visual field (VF) deterioration in eyes where all IOP readings over a six year period were below 18 mmHg (6); by contrast, VF significantly declined in eyes where IOP below 18 mmHg was recorded in less than 50 percent of visits. Patients with no progression had a mean IOP of 12.3 mmHg.

Is 24-hour IOP assessment useful in the real world? Prof. Quaranta is cautiously optimistic: "In normal clinical practice, it's not an option. Nevertheless, some specialized centers can accommodate 24 hour-monitoring. For select patients, these facilities can identify IOP peaks falling outside normal office hours, which could completely change the treatment approach." Indeed, where the data exist, they can make a real difference to patient management (Figure 8). Prof. Quaranta also suggests that monitoring both IOP and blood pressure over 24 hours is useful. "Where ocular perfusion pressure is increasing at night, we must take particular care to control IOP."

"Knowledge of 24-hour IOP patterns and 24-hour efficacy of glaucoma medications will help us tailor therapy for each patient."
- Luciano Quaranta.

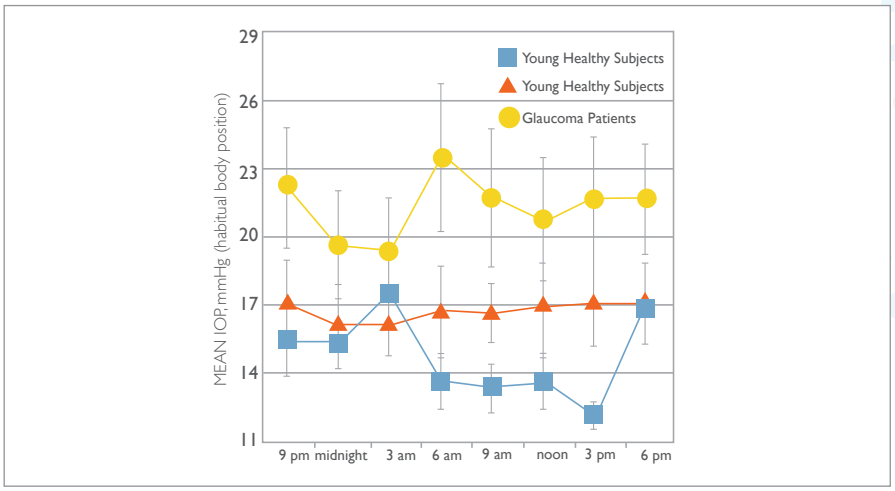

Figure 6. Estimating IOP at night-time. Collection of supine and sitting office-hour measurements may be an acceptable night-time surrogate in most cases.

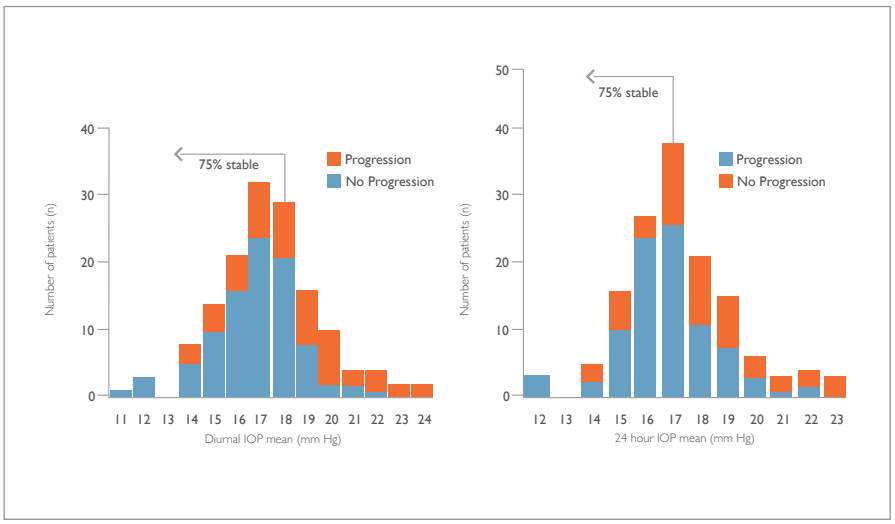

Figure 7. Relationship between disease progression and 24-hour IOP values. The magic number? Patients whose IOP does not exceed 18 mmHg usually do not exhibit disease progression.

New findings from 24-hour studies

It has gradually become more evident that many glaucoma patients suffer from ocular surface disease (OSD) due to long-term use of topical therapies. Preservative-free drops are generally thought to provide better tolerability and ocular surface health, says Prof. Konstas – yet we have little data on their efficacy. To investigate this point, Prof. Konstas and colleagues evaluated the 24-hour efficacy of PF tafluprost compared with latanoprost in newly diagnosed patients with POAG or OHT in a cross-over study. Three months of therapy were followed by habitual 24-hour monitoring; the top-line finding (7) was that there was no statistically significant difference between PF tafluprost and latanoprost in mean 24-hour IOP. However, PF tafluprost provided more consistent IOP control with less fluctuations over the 24 hour period. A follow-up study of the 24-hour efficacy of PF tafluprost in POAG patients with ocular surface disease

provided evidence that PF tafluprost has statistically significantly better 24-hour efficacy compared to preserved latanoprost in patients with signs and symptoms of ocular surface disease (OSD) (Figure 9), being associated with a greater reduction in mean, peak and fluctuation of 24-hour IOP, including at the 02:00 and 06:00 time points (8). This difference in efficacy may be attributed to the concomitant improvement in ocular surface health and tolerability of PF-tafluprost.

Extended IOP studies are also useful for comparing different treatment options: Prof. Konstas cites his collaboration with Prof. Quaranta and others (9) in which the 24-hour efficacy of dorzolamide-timolol fixed combination (DTFC) was compared with that of the brimonidine/timolol fixed combination (BTFC) in POAG. "Initial evidence from morning and daytime IOP readings had suggested BTFC was equal or superior to DTFC in terms of daytime efficacy – we wanted to know more." And the results? "In fact, DTFC was significantly more effective than BTFC – the difference is due to a reduced efficacy of BTFC in the late afternoon and during the night." Prof. Konstas reiterates that only 24-hour studies can provide this kind of insight.

Conclusions

We still don't know the precise characteristics of 24-hour IOP, says Prof. Quaranta. Nevertheless, it is clear that IOP fluctuates in a circadian way such that peak IOP occurs in the night or morning. These changes are driven by postural effects, geographical influences, ocular and systemic diseases, ageing and probably other factors

Available measurement methods have limitations and may not be attractive for patients (nor ophthalmologists). Nevertheless, says Dr. Figueiredo, they can provide important information to guide treatment -- he cites one study showing

Box 1. Clinical management guided by Icare data: two cases from the clinic of Antonio Figueiredo

Case 1

- Male, 64 years: exfoliation syndrome in left eye; IOPs of 15-17 mmHg Goldmann; normal visual fields but suspicious optic discs in left eye
- Self-monitoring indicated huge peaks and fluctuations between 5 am and 7 pm – sometimes double the ocular pressure observed during the day
- Direct comparison with Goldmann tonometry at 10 am, 12 am and 10 pm showed good agreement between the measurement systems
- OCT confirmed the IOP findings and showed up significant left eye structural changes that had occurred during the two years since the last examination
- Outcome: we are re-evaluating therapy for this patient

Case 2

- Male, 38 years, high myope, history of refractive surgery, glaucoma detected in 2010
- IOP went from ~18 mmHg in 2012 to ~30 mmHg in 2013 – probably related to topical corticoids
- IOP apparently controlled with fixed combination prostaglandins – but visible fields had badly deteriorated
- Additional examinations – blood pressure, neurological, ophthalmological – were normal, but disease seemed to be progressing
- This suggested that the patient was a candidate for surgery – but surgical options were aggressive/risky, refused by patient
- Therefore, IOP was monitored over 24 hours to determine extent of control: at all time points IOP was below 10 mmHg
- Outcome: IOP was well controlled, therefore surgery was unnecessary, and the patient could continue with current treatment

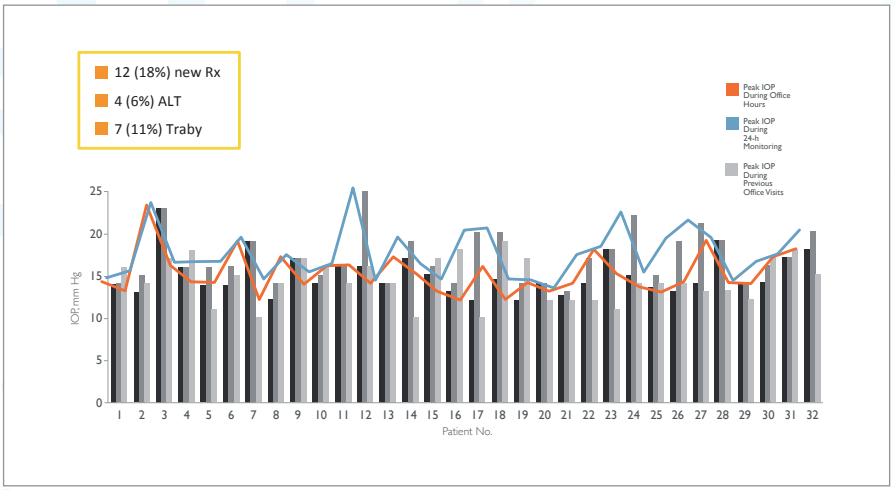

Figure 8. Clinical utility of 24-hour IOP monitoring. Monitoring 24-hour IOP in glaucoma patients guides treatment decisions towards new therapies or surgery.

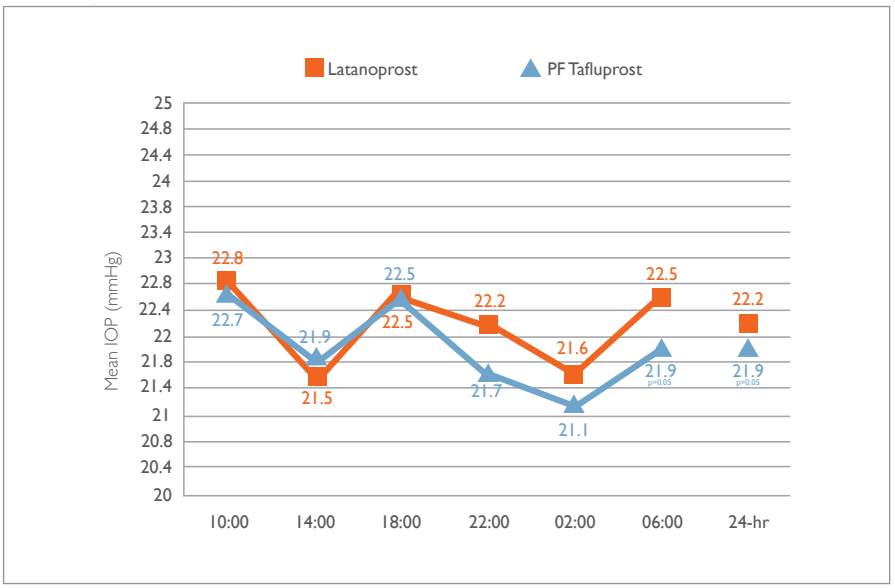

Figure 9. 24-hour IOP control: latanoprost versus PF tafluprost. PF tafluprost mediates IOP reduction superior to that of latanoprost over 24 hours (8).

that 24-hour IOP control studies led to clinicians changing therapy in 36 percent of eyes (59 percent of patients) (10).

Prof. Konstas reiterates that 24-hour IOP control may require drugs and dosing regimens to be optimized for best therapeutic effect. He reminds us of the growing body of published 24-hour IOP data that can guide choices in stepwise glaucoma therapy. We still have a way to go, however: Prof. Quaranta suggests that future work should include investigation of the relative value of different IOP characteristics – means, peaks, degree of fluctuation – in predicting glaucoma progression. Moreover, he recommends establishing optimal target 24-hour IOP values that can stabilize function at the early, moderate and late stages of glaucoma, respectively.

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Product Name: SAFLUTAN® tafluprost 15 micrograms/ml eye drops, solution in single-dose container.
Composition: Eye drops, solution, single-dose container (eye drops). A clear, colourless solution. One ml of eye drops, solution, contains 15 micrograms of tafluprost. One single-dose container (0.3 ml) of eye drops solution, contains 4.5 micrograms of tafluprost. One drop (about 30 microlitres) contains about 0.45 micrograms of tafluprost. Please refer to Summary of Product Characteristics (SmPC) for a full list of excipients.
Indication: Reduction of elevated intraocular pressure in open angle glaucoma and ocuar hypertension. As monotherapy in patients who would benefit from preservative free eye drops: insufficiently responsive to first line therapy: intolerant or contra-indicated to first line therapy. As adjunctive therapy to betablockers. SAFLUTAN® is indicated in adults >/= 18 years.
Posology and method of administration: The recommended dose is one drop of SAFLUTAN® in the conjunctival sac of the affected eye(s) once daily in the evening. The dose should not exceed once daily as more frequent administration may lessen the IOP lowering effect. For single use only, one container is sufficient to treat both eyes. Any unused solution should be discarded immediately after use. Use in elderly: No dosage alteration in elderly patients is necessary. Paediatric population: The safety and efficacy of tafluprost in children below age 18 has not yet been established. No data are available. Use in renal/hepatic impairment: Tafluprost has not been studied in patients with renal / hepatic impairment and should be used with caution. Method of administration: To reduce the risk of darkening of the eyelid skin patients should wipe off any excess solution. As with any eye drops, nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route. If more than one topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart.
Contraindications: Hypersensitivity to tafluprost or to any of the excipients.
Warnings and precautions: Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation. Some of these changes may be permanent, and may lead to differences in appearance between the eyes when only one eye is treated. The change in iris pigmentation occurs slowly and may not be noticeable for several months. The change in eye colour has predominantly been seen in patients with mixed coloured irises, e.g. blue-brown, grey-brown, yellow-brown and green-brown. There is potential for hair growth to occur in areas where tatluprost comes repeatedly in contact with the skin surface. There is no experience with taflupros in neovascular, angle-closure, narrow-angle or congenital glaucoma. There is only limited experience with tafluprost in aphakic patients and in pigmentary or pseudoexfoliative glaucoma. Caution is recommended when usng tafluprost in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oederna or iritis/ uveitis. There is no experience in patients with severe asthma. Such patients should therefore be treated with caution
Interactions with other medicinal products: No interactions are anticipated in humans, since systemic concentrations of tafluprost are extremely low following ocular dosing. Specific interaction studies with other medicinal products have not been performed with tafluprost. In clinical studies tafluprost was used concomitantly with timolol without evidence of interaction.
Fertility, pregnancy and lactation: Women of childbearing potentiallcontraception: SAFLUTAN® must not be used in women of childbearing age/potential unless adequate contraceptive measures are in place. Pregnancy: There are no adequate data from the use of tafluprost in pregnant women. Tafluprost can have harmful pharmacologic effects on pregnancy and/or the fetus/ newborn child. SAFLUTAN® should not be used during pregnancy unless clearly necessary (where no other treatment options are available). Breast-Feeding: It is unknown whether tafluprost or its metabolites are excreted in human milk. Tafluprost should not be used during breast-feeding.
Ability to drive and use machines: Tafluprost has no influence on the ability to drive and use machines. As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.
Undesirable effects: In clinical studies with preserved tafluprost the most frequently reported treatment related adverse event was ocular hyperaemia in approximately 13% of patients. It was mild in most cases and led to an average 0.4% discontinuation. In a 3-month, phase III study comparing the non-preserved formulation of tafluprost with the non-preserved timolol formulation, ocular hyperemia occurred in 4.1% (13/320) of patients treated with tafluprost. The following undesirable effects related to treatment were reported during clinical trials with tafluprost after a maximum follow-up of 24 months: within each frequency grouping, adverse reactions are presented in order of decreasing frequency. Nervous system disorders: Common (>/=1/100 to <1/10); headache Eye disorders: Common (>/= 1/100 to <1/10): eye pruritus, eye irritation, eye pain, conjunctival / ocular hyperemia, changes in eyelashes (increased length, thickness and number of lashes), dry eye, eyelash discolouration, foreign body sensation in eyes, erythema of eye lid, superficial punctate keratitis (SPK), photophobia, blurred vision, increased lacrimation, reduced visual acuity and increased iris pigmentation. Uncommon (>/=1/100) to <1/100): blepharal pigmentation, eyelid oedema, asthenopia. conjunctival oedema, eye discharge, blepharitis, anterior chamber cells, ocular discomfort, anterior chamber flare, conjunctival pigmentation, conjunctival follicles, allergic conjunctivitis and abnormal sensation in eye. Frequency not known: iritis/uveitis, deepening of the lid sulcus, macular oedema /cystoid macular oedema. Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas. Respiratory disorders: Frequency not known: exacerbation of asthma, dyspnea. Skin and subcutaneous tissue disorders: Uncommon (>/=1/1,000 to < 1/100); hypertrichosis of eyelid. Please also see the SmPC. Overdose: Treatment should be symptomatic.
Special precautions for storage: Store in a refrigerator (2° -- 8°C). After opening the foil pouch keep the single dose containers in the original pouch and do not store above 25°C. Discard opened single-dose containers with any remaining solution immediately after use.
Package quantities: 30 x 0.3 ml single-dose containers. Low density polyethylene (LOPE) single-dose containers packed in foil pouch. Each single-dose container has a fill volume of 0.3 ml and there are 10 containers in each foil pouch.
MA Holder: Santen Oy, Niittyhaankatu 20, 33720 Tampera, Finland.
Price; 30 x 0.3ml single-dose containers; £12.20
MA number: PL 16058/0017. **Date of Authorisation:** 17/10/2008 **Legal Category:** POM
Date of prescribing infonnation: December 2017
Prescribing Information No:- NP-SAFLUT-UK-0006

Abbreviated Prescribing Information
Product Name: COSOPT® Preservative-Free 20 mg/ml + 5mg/ml, eye drops, solution, single-dose container.
Composition: Each millilitre contains 20 mg dorzolamide(22.26 mg dorzolamide hydrochloride) and 5 mg timolol (6.83mg timolol maleate). Please refer to the Summary of Product Characteristics (SmPC) for a full list of excipients.
Indication: Treatment of elevated intra-ocular pressure (IOP) in patients with open-angle glaucoma, or pseudoexfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.
Posology and Method of Administration: One drop of COSOPT Preservative-Free in the conjunctival sac of the affected eye(s),two times daily. If another topical ophthalmic agent is being used, administer COSOPT Preservative-Free and the other agent at least ten minutes apart. COSOPT Preservative-Free is a sterile solution that does not contain preservative. Solution from a single dose container should be administered immediately after opening and any remaining contents discarded immediately after use. Safety in paediatric patients less than 2 years of age has not been established. Please see the SmPC for use in children of more than 2 years.
Contraindications: Hypersensitivity to any component of thismedicine, reactive airway disease, including bronchial asthma,or a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, sick sinus syndrome, sino-atrial block, second- or third-degree atrioventricularblock not controlled with pacemaker, overt cardiac failure, cardiogenic shock, severe renal impairment (CrCl <30 ml/min)
Warnings and Precautions: The same types of adverse reactions found with systemic administration of beta-blockers
or sulphonamides may occur, these include severe reactions seen with sulphonamides such as Stevens-Johnson syndrome and toxic epidermal necrolysis. In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients should be watched for signs of deterioration and adverse reactions. Beta-blockers should only be given with caution to patients with first degree heart block. Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution. Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. Use with caution, in patients with mild/ moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk. Use with caution in patients with hepatic impairment. Concomitant use of dorzolamide with oral carbonic anhydrase inhibitors is not recommended. Use of two topical beta-adrenergic blocking agents is not recommended. Caution in patients subject to spontaneous hypoglycaemia or with labile diabetes. These signs and symptoms of acute hypoglycaemia and hyperthyroidism may be masked. Caution in patients with corneal diseases. The anaesthetist should be informed when a patient is receiving timolol as betablocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. Though no acid-base disturbances have been observed with COSOPT (preserved formulation), patients with a prior history of renal calculi may be at increased risk of urolithiasis. Patients with acute angleclosure glaucoma require therapeutic interventions in addition to ocular hypotensive agents. This medicinal product has not been studied with acute angle-closure glaucoma. There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. Precautions should be used when prescribing in these groups of patients. This medicinal product has not been studied in patients wearing contact lenses. There is limited experience with COSOPT Preservative-Free in infants and children. Please refer to the SmPC.
Interactions with Other Medicinal Products: There is a potential for additive effects resulting in hypotension and / or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, catecholamine-depleting drugs or beta adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, quanethidine, narcotics and monoamine-oxidase (MAO) inhibitors. Potentiated systemic beta-blockade (e.g. decreased heart depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol. Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.
Pregnancy and Breast Feeding: Do not use in pregnancy or during breast feeding.
Driving and using machines: Possible side effects such as blurred vision may affect some patients' ability to drive and/or operate machinery.
Undesirable Effects: (Refer to SmPC for complete information on side effects.) The side effects observed with COSOPT Preservative-Free or one of its components include: headache, depression, burning and stinging, conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing, eyelid inflammation, eyelid irritation, iridocyclitis, signs and symptoms of ocular irritation including blepharitis, keratitis, decreased corneal sensitivity and dry eyes and visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), ptosis, bradycardia, syncope, sinusitis, dyspnoea, dysgeusia, nausea and dyspepsia, urolithiasis, signs and symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis, asthenia/ fatigue, hypoglycaemia, cardiac arrest, heart block, AV block, cardiac failure, chest pain, palpitation, oedema.
Overdose: Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.
Special Precautions for storage: Do not store above 25 °C
Package Quantities: 60 x 0.2mL low density polyethylene single-dose containers in a foil sachet containing 15 or 10 single-dose containers.
Price: 60 x 0.2mL single-dose containers £28.59.
MA Holder: Santen Oy, Niittyhaankatu 20, 33720 Tampere, Finland. **MA Number:** PL 16058/0015
Date of renewal of the authorisation: 10 December 2008
Legal Category: POM
Date of Prescribing Information: May 2018. COSOPT® is a registered trademark of Santen PharmaceuticalsCo., Ltd.
Job Code: NP-CSPTPF-UK-0001

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Santen UK Limited (Email: medinfo@santen.co.uk or telephone: 0345 075 4863).

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