ORIGINAL ARTICLE

Glaucoma Therapy – Current Overview of Data and Information

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SUMMARY

The authors submit the overview of the actual situation in the glaucoma therapy. They follow up the trends in antiglaucomatic treatment in the last period including financial aspects of medicament and surgical treatment. Attention is paid especially to medicaments management, actual overview of available antiglaucomatic drugs, function and position of generic drugs and differences among them, the daily dose of benzalconium chloride in glaucoma treatment, actual average of patients' supplementary payments at the drug purchase in the pharmacy, surgical treatment costs and legal issues. Pharmacologist's viewpoints and the Czech State Drug Control Authority (SÚKL) opinions complete the professional's point of the view and facilitate his/her complete orientation in glaucoma therapy issues.

Key words: glaucoma, prescription, surgical treatment, treatment costs, legal issues

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INTRODUCTION

Glaucoma is a serious disease with a considerable socio-economic impact. New trends in diagnostics and therapy are substantially improving the chances of the patient and the doctor in the fight against this disease, and in avoiding its consequences. However, our level of knowledge and the possibilities in this area still lag behind expectations (9).

The aim of this message is to assist ophthalmologists in their decision-making in modern glaucoma therapy – to provide an overview of the therapeutic options, to summarise and comment on the available data for easier orientation therein, and to present partial conclusions.

The diagnostic methods and therapeutic procedures in the field of glaucoma are undergoing a phase of fascinating development. The basic groups of tasks in this field going into the future can be classified within four frames: successful diagnosis, timely diagnosis, timely detection of the progression of glaucoma and successful intervention in order to halt progression. The correlation of the information obtained by functional examination (by perimetry) and the data obtained upon morphological examination using imaging techniques is already being evaluated and addressed by clinical studies, but there is still a lack of exact processing of the direct impact in clinical practice. A range of analysts and clinical specialists at various workplaces are working on this issue. We expect results within the time frame of 5-10 years. Neuroprotective and gene therapy is also a matter for the future. The effectiveness of various options of alternative or supplementary therapy is so far unverified by randomised clinical studies.

The currently recommended diagnostic scheme for the glaucomatologist thus remains: complex eye examination including examination of central visual acuity, most preferably using ETDRS optotypes, examination of the field of vision by static perimetry, monitoring of intraocular pressure by Goldmann's applanation tonometry, gonioscopy, exact assessment of the finding on the disc of the optic nerve and examination by one of the available imaging techniques. In therapy it still applies that there is a choice of three options: conservative, laser or surgical treatment, or a combination thereof.

In the endeavour to provide clearly presented, current integrated information on the issue of glaucoma treatment, we have chosen the following model.

1. Management of pharmaceuticals
2. Overview of antiglaucomatous drugs available on 1 June 2013
3. Overview of prescription of antiglaucomatous drugs in the Czech Republic
4. Comparison of prescription of antiglaucomatous drugs in the Czech Republic and Slovak Republic
5. Significance and position of generics
6. Preservative agents – benzalkonium chloride in eye drops reducing intraocular pressure.
7. Other factors in deciding on the choice of glaucoma therapy
8. Glaucoma surgery – costs and comparison with conservative treatment
9. Conclusion
10. Literature

1. Management of pharmaceuticals

In 2011 pharmaceuticals with a value of more than CZK 1.5 billion remained without real use, and people either returned them to pharmacies, disposed of them in municipal waste or returned them to doctors' surgeries. On an overall scale this concerns at minimum 3.7% of all deliveries of distributors of pharmaceuticals. This ensued from the research conducted by the State Institute for Drug Control (SÚKL) "Real use of pharmaceuticals and its financial impact on the healthcare system in the Czech Republic", which was conducted by the STEM/MARK agency (see http://www.sukl.cz). An audit of first aid kits in Czech households in 2000 demonstrated that 20% of drugs are unused and 12% of drugs are past their use by date. The average number of packages of pharmaceuticals per household is 17, of which 41% comprise prescription drugs. Only 53% of households return unused pharmaceuticals to a pharmacy, 29% dis-

card drugs in municipal waste and 15% of households accumulate drugs at home and do not address their liquidation. The most frequent reason for discarding pharmaceuticals is that they are past their use by date, and the absence of the person for whom the drugs were originally intended – due to moving house, death etc. It is necessary to spend further hundreds of millions of Czech crowns on the ecological liquidation of pharmaceuticals which are discarded in waste. Regions pay from 12 to 48 thousand Czech crowns per 1 ton of this material in hazardous waste incinerators, and the total financial costs for 245 tons of unused drugs with a value of one billion Czech crowns in 2011 came to 7.5 million Czech crowns. It is entirely possible to find reserve capacities for how to be more economical in this respect, on the part of both patients and doctors.

2. Overview of antiglaucomatous drugs

The following overview presents a structured outline of the antiglaucomatous drugs available in the Czech Republic to the date of 1 June 2013, for better orientation stating the holder of the marketing authorization according to the SPC(= Summary of Product Characteristics) or distributor.

Adrenergic agonists - brimonidine
ALOHAGAN (Allergan)
LUXFEN (Jelfa – Valeant Pharma)

Beta-blockers
- **Non-selective** – timolol, levobunolol
TIMOLOL POS (Ursapharm)
▌TIMO COMOD (Ursapharm)
▌ARUTIMOL (Chauvin Ankerpharm – Bausch and Lomb)
▌TIMOPTOL (Merck Sharp Dohme)
▌TIMOHEXAL (Sandoz – Novartis)
▌UNITIMOLOL (Unimed Pharma)
▌OFTAN TIMOLOL (Santen)
▌VISTAGAN (Allergan)
- **Selective** – betaxolol
▌BETOPTIC, BETOPTIC S (Alcon – Novartis)
▌BETALMIC (Unimed Pharma)
- **With internal sympathomimetic activity** – carteolol
▌CARTEOL LP (Mann – Bausch and Lomb)
▌ARTEOPTIC (Laboratories Thea)

Cholinergic drugs – pilocarpine
▌PILOGEL HS (Alcon – Novartis)

Carboanhydrase inhibitors
- **Local** – brinzolamide 1% AZOPT (Alcon – Novartis)
▌dorsolamide 2% TRUSOPT (Merck Sharp Dohme)
▌OFTIDOR (Jelfa – Valeant Pharma)
- **application per os** – acetazolamide DILURAN (Zentiva)
- **application intravenously** – MANITOL 15% VIAFLO (Baxter)

Prostaglandin analogues
▌latanoprost 0.005% - XALATAN (Pfizer)
▌travoprost 0.004% - TRAVATAN (Alcon – Novartis)
▌bimatroprost 0.03% - LUMIGAN (Allergan)
▌alfuprost 0.0015% - TAFLOTAN (Santen)

latanoprost generics:
▌ARULATAN (Chauvin Ankerpharm – Bausch and Lomb)
▌GLAUCOTENS (Valeant Czech – Valeant Pharma)
▌LATALUX (Glimcare – Valeant Pharma)
▌LATANOPROST ACTAVIS (Actavis – Watson)
▌LATANOPROST APOTEX (Apotex)
▌LATANOPROST POS (Ursapharm)
▌LATANOPROST RATIOPHARM (Ratiopharm – TEVA)
▌SOLUSIN (Genericon)
▌UNILAT (Unimed Pharma)
▌XALOPTIC (Polpharma)
▌ZELEZA (VULM CZ)

Combination with timolol
+ pilocarpine (beta-blocker + miotic)
▌FOTIL, FOTIL FORTE (Santen)
+ dorzolamide (beta-blocker + ICA)
▌COSOPT (Merck Sharp Dohme)
▌DORZOGEN COMBI (Mylan Generics)
▌DORZOLAMID / TIMOLOL (TEVA)
▌DOZOTIMA (Valeant – Valeant Czech)
+ brinzolamide (beta-blocker + ICA)
▌AZARGA (Alcon – Novartis)
+ latanoprost (beta-blocker + PG)
▌XALACOM (Pfiter)
▌GLAUCOTIMA (Valeant – Glimcare)
▌LATANOPROST / TIMOLOL (Apotex)
+ bimatoprost (beta-blocker + PG)
▌DUOTRAV (Alcon – Novartis)
+ brimonidine (beta-blocker + adrenergic agonist)
▌COMBIGAN (Allergan)

3. Overview of prescription of antiglaucomatous drugs in the Czech Republic in 2011 and 2012

New pharmaceuticals are coming onto the market, namely generics of latanoprost for which the inter-year increase is not stated for this reason (N/A). Latanoprost Ratiopharm, which had the advantage of being introduced onto the market first, is already beginning to lose its lead. We are at the beginning of a phase in which the number of patients for whom treatment of glaucoma by monotherapy is indicated is divided at the physician's discretion between literally dozens of options. The accession of Taflotan is favourable. With regard to the advantage that it does not contain preservative agents, it is very well tolerated also by the group

Table 1. Prescription of prostaglandin analogues in glaucoma therapy in the Czech Republic in 2011

	Number of packages (thousand items)	Inter-year growth (%)	Price (million CZK)
Xalatan	99 000	-1	69
Travatan	43 000	-16	33.5
Lumigan	32 000	-2.5	24
Taflotan	5 000	N/A	4.5
Latanoprost Ratiopharm	30 000	-10	6.6
Unilat	9 000	N/A	3.7
Latanoprost Actavis	4 600	N/A	3
Solusin	3 000	N/A	1.6
Xaloptic	1 400	N/A	0.3

Table 2. Prescription of fixed combinations in glaucoma therapy in the Czech Republic in 2011

	Number of packages (thousand items)	Inter-year growth (%)	Price (million CZK)
Cosopt	35 000	+9	27
Ganfort	25 000	+3	22.5
Combigan	60 000	+3	16
Duotrav	13 000	+12	13.5
Xalacom	21 600	+22	13
Fotil	20 000	+58	

of patients who hitherto had complaints regarding tolerance of therapy and compliance. Another feature is that the costs for the original pharmaceuticals of this group are decreasing (Xalatan – 13%, Travatan – 18%), because the accession of generics is leading to a reduction of reimbursement both in legislative form and due to the distributor's decision with regard to the improved ability of the competition (Table 1).

In 2011 the prescription of fixed combinations increased (Table 2). The highest rung in terms of costs was occupied by Cosopt, the largest number of packages is for Combigan.

Of the pharmaceuticals not listed in the table, Azopt has a considerable share in the number of dispatched packages (230 thousand items, inter-year growth of +7%, with a value of CZK 46 million). These figures are highly influenced by the re-export of pharmaceuticals (see below). The number of packages of Trusopt is 10x lower. The relation between Alphagan and Luxfen is also interesting – there was more than 50% decrease in the prescription of Alphagan (to 16 thousand packages) in comparison with a doubling of the prescription of Luxfen (to 33 thousand packages). In this the costs for both items are identical – CZK 3 million.

In the group of beta-blockers, the downward trend continued – a reduction in the prescription of Timoptol, Arutimol, Unitimolol, Oftan Timolol by 10-12%. A slightly less significant reduction was recorded by Timolol POS (-6%) and TimoCOMOD (-5%). The most significant share on the beta-blockers market has been occupied for a number of years by the drugs Betoptic and Betoptic S (altogether almost 200 thousand packages, inter-year decrease of -3%, costs CZK 13 million).

Overview of the prescription of ophthalmologic drugs (S01) and antiglaucomatous drugs (S01E2) in 2012.

In 2012, 5 542 355 packages of ophthalmologic drugs were prescribed (inter-year decrease of -2.6%) at a price of CZK 647 571.2 thousand (inter-year growth of +8.5%). In the group of antiglaucomatous drugs, 1 294.9 thousand packages were dispatched (inter-year growth of +8.4%) at a price of CZK 390 802.8 thousand (inter-year growth of +11.5%). However, these figures are not as remarkable as they may seem at first sight in comparison with the treatment of other diseases. On the contrary, the costs for the group of "Sensory organs" are somewhat surprisingly as low as in the 11th place in terms of the cost of treatment according to groups of illnesses. Above the treatment of sensory organs in the table of costs are treatments for the cardiovascular system, CNS, digestive tract, respiratory system, urological and sexual disorders, costs for anti-neoplastic and immunomodulation therapy, disorders of the locomotor system, treatment of systemic infections, treatment of blood disorders and dermatological treatment. Lower costs are only for systemic hormonal treatment, medical liquids, parasitological therapy and diagnostic preparations. From the above it ensues that the treatment of eye disorders is certainly not as costly as is often attributed to ophthalmologists at various discussions.

Table 3. Overview of prescription of selected antiglaucomatous drugs in the Czech Republic in 2012

	Number of packages (thousand items)	Inter-year growth (%)	Sale (thousand CZK)	Inter-year difference
Xalatan	114.5	+16.1	67 610.7	-2.4
Xalacom	25.5	+17.9	26 500.7	+28.6
Azopt	275.2	+21.5	57 230.6	+24.4
Travatan	80.2	+87.4	52 133.7	+55.7
Cosopt	38.1	+7.9	30 478.8	+13.3
Combigan	39.2	-34.6%	8 112.4	-49.3
Lumigan	24.2	-24.7	18 328.4	-23.8
Fotil	37.8	+94.3	5 276.1	+113.0
Taflotan	5.8	+21.8	-5 234.2	+15.5
Latanoprost	21.7	-27,1	4 229.5	35.9
Ratiopharm				

The increase in the prescription of Xalatan by more than 16% is a favourable feature and signals a return to the original molecule. The reasons are technical, and additionally facilitated by the decision of the distributor to reduce the costs for the surgery of a doctor-specialist (Table 3).

It is impossible to overlook the dramatic increase in the dispatch of Azopt (+21.5%) and especially Travatan (+87.4%). In searching for the reason for this phenomenon it is possible to determine that there is no technical connection here which would justify a higher prescription. With regard to the legislative regulation, this figure is substantially increased by "re-export". Some drugs are considerably cheaper in the Czech Republic than in the neighbouring countries of the European Union, so for traders this is a clear signal for purchasing them here. It therefore represents a merely economic matter, which however may have negative impacts on the availability of a particular pharmaceutical for our patients. This has already been manifested in areas other than ophthalmology, but in future we may encounter it also in our field.

A problem of prescription of Combigan and also Cosopt is the very high supplementary payments for the patient – as the situation develops further this shall rather be an issue for the distributor, because we do not expect any resolution to the problem on the part of the state administration.

The decrease in the prescription of Latanoprost Ratiopharm (-27%) is linked partially to the fact that the option of choice between generics of latanoprost increased, but also because here we see the full manifestation of the access of a number of generic firms which as a rule have been addressing the situation within the time frame of only a few years. It is necessary to reckon with their possible strategy: we shall have another generic in another field, the company or the distribution rights to the drug are sold.

The prescription of Fotil showed an inter-year increase of 94.3%. The explanation is simple, but all the sadder for it. With regard to the discontinuation of the prescription of miotics (pilocarpine) in the original packaging, ophthalmologists are forced to resolve the situation either by ensuring magistraliter prescription of pilocarpine, which is not always and everywhere a simple matter, or by prescription of Fotil, which however contains not only miotics but also a beta-blocker, which in a range of specific cases is contraindicated. All efforts to communicate with regard to this matter between experts and pharmaceutical firms have unfortunately remained without a specific response.

How can we evaluate this situation briefly and politely? The commercial perspective has predominated over professional interests and even over years of co-operation. No difference to this situation has been made even by the fact that the therapeutic portfolio with which both parties have worked for years was very wide. The current recommendation is the possibility of prescribing Pilogel – however, this represents only a single delivery as a result of addressing the problem of the insufficient amount of miotics between the Czech Ophthalmological Society, the Czech Glaucoma Society and the distributor. In future it is not possible to rely on the prescription of this drug in the Czech Republic, and it is necessary to seek further solutions for patients with narrow angle glaucoma. According to the statistics, this represents approximately 10 % of patients with glaucoma, and this therefore means that the problem is not negligible.

There is a sympathetic inter-year increase in the indication of Taflotan by more than 1/5 (+21.8 %). For us the fundamental standpoint in an evaluation of this situation is the resolution of those conditions in which the patient is finally rid of undesirable side effects of preservative agents after trying a whole range of medicamentous therapy.

4. Prescription of antiglaucomatous drugs in the Slovak Republic – comparison with prescription in the Czech Republic

Upon an analysis of the summary data on the quality and quantity of prescription of antiglaucomatous drugs in the Slovak Republic and the Czech Republic in 2010 and 2011, clear differences were found between the composition of prescribed drugs in both countries and also in the trends of treatment in the observed time period (4, 8).

In 2010, 1.23 million packages in the group of antiglaucomatous drugs were distributed in the Czech Republic (22 % of packages of ophthalmologic drugs in total), with a turnover of CZK 600 million. Largest number of packages: Azopt (211 thousand), Betoptic (89 thousand) + Betoptic S (122 thousand), Xalatan (97 thousand). In 2011 the total number of prescribed antiglaucomatous drugs remains without a marked change, only with a slight increase in turnover. There were increases in the prescription of Azopt (227 thousand), Xalatan (99 thousand) and Taflotan at the expense of Travatan and Lumigan, only a slight increase in Cosopt and Xalacom, no significant change in Combigan and Ganfort and a decrease in Betoptic.

In the Slovak Republic a striking discovery is the inter-year decrease in the prescription of prostaglandin in monotherapy and the preference for combined therapy – in 2010 Xalatan – 20%, Travatan – 8%, Cosopt +14%, Combigan +4%, largest numbers of prescribed packages: Cosopt (109 thousand), Xalatan (98 thousand), Azopt (80 thousand. In 2011 there was an increase in the prescription of Cosopt (133 thousand), Xalatan (111 thousand), Azopt (87 thousand), Xalacom (49 thousand), Unilat (31 thousand), Ganfort (19 thousand), no significant change in the prescription of Combigan and a further decrease in Travatan and Lumigan.

In total EUR 7 180 000 was spent on antiglaucomatous medication in 2012. In comparison with the previous year this represents an inter-year increase of +1.7%. This amount constitutes 52.6% of costs for all ophthalmologic drugs.

The described trends continued also in 2012, although the increase in the prescription of fixed combinations was slower (Cosopt, Ganfort) or without change (Combigan, Xalacom, Duotrav). In monotherapy using prostaglandin analogues we determined a decrease in the prescription of Xalatan, Travatan, Lumigan, an increase in Unilat and also an increase in Azopt and Pilocarpine. Taflotan is also beginning to claim its place on the market (3 000 items, EUR 32 600) (Table 4). The current portfolio of antiglaucomatous drugs in the Czech and Slovak Republics naturally differs. In Slovakia, for example, Alphagan is not available but Brimonal is offered, Timolol POS and Timohexal are absent, miotics and also Cosopt free (without preservative agents) are ordinarily available.

5. Significance and position of generics

How do pharmacologists view this issue?

Rationally managed pharmacotherapy has an entirely fundamental influence on life expectancy – this has increased from 78.5 to 79.9 years. It is precisely access to new medicaments that has contributed to this increase to the extent of at least one third. This increase was most evident in countries with a higher consumption of pharmaceuticals. An interesting view is provided by the statistics of the General Health Insurance Company, where – despite media proclamations – the costs of drugs are surprisingly not increasing significantly. In recent years it is in fact possible to observe a slight reduction in the case of prescription drugs. However, in contrast with this costs are increasing e.g. for outpatient healthcare or spa residences (2).

What is the path of generic drugs onto the market? In observing this, it is necessary first of all to describe all the attributes in connection with the inception of the original pharmaceutical. The development of a new pharmaceutical is a very complex process. From an original number of 5-10 thousand molecules, approximately 10 enter a clinical trials and approximately one enters the marketing authorization process. This process is very lengthy, stated within the range of 10+15 years (3-6 years pre-clinical research, 5-7 years clinical research, 0.5-2 years marketing authorization). Clinical research is composed of phases I-IV: in phase I the drug is tested on a small group of healthy volunteers, in phase II on a small group of ill patients, and in phases III and IV on large groups of ill patients, in which the trial is very often controlled with a placebo, or the effectiveness of the active ingredient is compared with another active comparator. Although patent protection is 20 years, it dates from the moment of discovery of the particular specific molecule, not from the moment of introduction of the pharmaceutical onto the market. In recent years we can observe a trend of a significant increase in the costs in connection with the development of a new drug. Whereas in 1979 this price was estimated at approximately 100 million US dollars, in 2005 this represented more than 1.3 billion US dollars. By far the most expensive item is clinical studies within the framework of the development (phase II). According to the Association of Innovative Pharmaceutical Industry (AIFP), costs for science and research are almost 8x higher than the average proportion of these expenditures in the Czech Republic, and substantially exceed even traditional industrial sectors – e.g. the automobile industry. The member companies of the AIFP employ thirty times more employees in science and research than the average in the Czech Republic. In 2009 costs for the development in the Czech Republic came to 1.2 billion Czech crowns. In the same year, an amount of 156 billion Czech crowns was paid to the State Institute for Drug Control in various administrative fees.

Research and development of a new pharmaceutical is a very complex process, in which the actual production takes place under strict conditions of good manufacturing practice (GMP). The process is strictly controlled at a chemical and analytical level. For example, during its development and post-marketing ob-

servation the preparation Xalatan was tested in 98 clinical studies, in which a total of 62 670 patients participated.
As the composition of adjuvant substances (excipients) in the original and in the generic may differ markedly, differences may be manifested in tolerance or the occurrence of adverse reactions. The solubility, efficacy and penetration of the active ingredient may be influenced. Particular particles may increase eye irritation; differences in viscosity and tension may lead to blurred vision. In the case of generics there is often insufficient evidence from clinical studies on safety and insufficient data from long-term use. According to the directives of the European Medicines Agency (EMA), however, it is possible to request a "biowaiver", or exception, in the case that a generic medicament is registered by the national marketing authorization procedure without any further studies, only on the basis of demonstration of the identical content.
Does a representative of a pharmaceutical company enter surgery with the statement "We have a study!"? Ask where this study is located according to the hierarchy of demonstrable facts. This is determined according to the following scheme – clinical experience, case report, case series, cross-sectional analysis, case control, cohort, controlled, prospective randomised control trial (RCT). It may concern a marketing study which often may not have a sufficient predicative value.
A comparison of the efficacy and safety profile of the original and the generic is at the centre of interest of patients and doctors, not only in the field of glaucoma, but also in treatment with antibiotics, steroids or non-steroid antiphlogistics. In the period of the expiring patent protection of the original molecule, the relevant state drug registration authorities (e.g. the FDA in the USA, the SÚKL in the Czech Republic) are inundated with requests.
Whereas in the USA and other countries a very substantial difference in price is evident between the original and a generic product, in the Czech Republic, due to the system of referential reimbursements, the lower price of the newly introduced generic is of determining significance for the price of the original. From the perspective of the payer or the savings in the healthcare system, the pressure to use a generic alternative is not so pronounced. In this, with regard to the different composition of adjuvant substances, it is possible to expect also different clinical efficacy. From a purely practical perspective, it is therefore possible to state that with regard to the existing system of prices and reimbursements in the Czech Republic, in which reimbursement relates to the active ingredient, within the context of the above it is more advantageous to choose the original product, although the valid legislation considers it to be interchangeable with generic products.

How do ophthalmologists view this issue?
As the fundamental set of official information on the product, professionals are served by the summary of product characteristics, the professional publications including case reports (3), whilst laypersons are served by the package information leaflet about the drug. From a lay perspective, however, this package information leaflet contains too much overwhelming data, which discourages laypersons from reading it, or due to the size of the lettering some patients are not even capable of reading the miniature text. From a legal perspective, however, the majority of this information must be presented here. Detailed knowledge of these documents is expected from the prescribing doctor, who is obliged to familiarise patients with all the possible risks before the commencement of treatment. What can be deduced from these documents? Amongst other factors, data on where the drug is manufactured and where it is registered. Also for example the fact that paediatric indication of prostaglandin analogues is approved only in the case of Xalatan and Latanoprost POS. A whole range of pharmaceuticals can be indicated only for patients over the age of 18 years, and not during pregnancy or breastfeeding. The drug may cause defocusing of vision, eye infections – conjunctivitis, reduction of sensitivity of the eye to touch, may affect ability to drive a motor vehicle and operate machinery, may cause swellings of the cornea, sinusitis, loss of appetite, epistaxis, in rare cases Peyronie's disease, in breastfed rat offspring it is the cause of slower weight gain of the young, a teratogenic effect is described in rabbits, or a progression in poisoning upon oral use. In a thorough study of package information leaflets it is possible to determine also the fact that it is necessary to store a specific pharmaceutical in the box throughout the entire period of use, and also that in order to attain efficacy in monotherapy it is applied 3x daily.

6. Preservative agents – daily dose of benzalconium-chloride in glaucoma therapy

Depending on concentration, the presence of preservative agents in eye drops can have a cytotoxic effect on the cells of the cornea and the conjunctiva, and can also cause objective complaints to patients (1, 5, 7, 9). As a result, a comparison of the concentration of benzalconium-chloride (BAC) in the particular products used in glaucoma therapy is highly interesting. The most significant criterion in this observation is the calculation of the daily dose of BAC for individual antiglaucomatous drugs on the basis of the size of the drop and the concentration of BAC. Data has been obtained by the method described in our previous work on this theme (7). In cases where this was necessary, calculations were performed on the basis of a verification of the current average content in a number of packages. According to the chosen therapy, the daily dose of BAC differs widely – from 0 to 10 micrograms. The concentration of BAC is one of the most important factors influencing compliance of the patient in the treatment of primary open angle glaucoma. The daily dose of BAC in the individual pharmaceuticals used in glaucoma therapy is not insignificant, and it is necessary to take into consideration the potential complications in connection with the content of this preservative agent in the therapeutic balance in the interest of good co-operation of the patient. The frequency of application of pharmaceuticals was calculated according to SPC. We present an overview of the daily doses of BAC in beta-blockers and alpha-mimetics (Table 5). The overview shall be supplemented by prostaglandin analogues, carboanhydrase inhibitors and fixed combinations, and shall subsequently be published separately. A calculation of the data for all generics and their verification is also being conducted, with a subsequent request for a statement from the relevant distributors. In the case of several new medicinal products a higher daily dose of BAC was calculated in comparison with the expectation.
Glaucoma and dry eye syndrome frequently occur together – according to estimates up to 60% of glaucoma patients have dry eye syndrome. It has been demonstrated that BAC used as s preservative agent in antiglaucomatous drops causes and aggravates dry eye syndrome. In an endeavour to improve the quality of life and compliance of glaucoma patients, for example BAC-free drops have been developed, or the use of nanotechnologies has been introduced. Cationic oil-in-water nanoemulsions represent a new type of preservative-

-free carriers of eye medications with properties protecting the eye. They contain positively charged oil nanodroplets of a size of 200 nm, dispersed in an iso-osmolar to lightly hypo-osmolar aqueous phase. These oil nanodroplets, through their interaction with the negatively charged epithelium of the surface of the eye, help improve the effect of the eye drops. These interactions contribute to the stabilisation of the lachrymal film – increase in BUT in patients with dry eye syndrome treated with Cationorm (Novagali Pharma, Evry, France).

Catioprost (Novagali Pharma) is a preservative-free cation nanoemulsion of oil in water, in which the oil nanodroplets contain latanoprost (0.005%). Pre-clinical studies demonstrate that this therapy is equally as effective as Xalatan in an ape model of increased intraocular pressure, and is very well tolerated in a model of the surface of rabbit eyes – 42% reduction of the incidence of hyperaemia in comparison with Xalatan. Upon affliction of the corneas in a rat model, following erosion and therapy for a period of twice a day with Catioprost – a healing of the cornea is described without scars, whereas after Xalatan and its carriers a significant opaque corneal scar formed beneath the healed epithelium. Catioprost is superior to BAC-free antiglaucomatous therapy in glaucoma patients with dry eye syndrome (1, 5).

Upon deciding on the therapy, however, it is not possible to be directed only by the presented figures or plans for the future – glaucoma therapy is complex, long-term and requires an individual approach.

7. Other factors in deciding on the choice of glaucoma therapy

Marketing authorization procedure and post-marketing surveillance of eye products – how does SÚKL view this issue?

The State Institute for Drug Control (SÚKL), which assesses the quality (composition, quantity and types of impurities, physicochemical properties of the medicinal product, manufacturing procedure), efficacy and safety of a medicinal product by means of demonstrated scientific publications, in vitro and in vivo studies, clinical and bioequivalent studies conducted by the applicant, is responsible for marketing authorization of pharmaceutical products in the Czech Republic.

The majority of eye preparations are currently registered as generics in the Czech Republic. This means that they must fundamentally resemble the referential product (original), the efficacy and safety of which has already been demonstrated. The development of a generic eye preparation is governed by the Note for Guidance on the Clinical Requirements for Locally Acting, Locally Applied Medicinal Products Containing Known Constituents. Eye preparations fall within the category of locally acting preparations, meaning that they act only in the area of application, and any systemic action is considered to be an adverse drug reaction. In the case of suspicion of systemic absorption from the place of application, the applicant must substantiate the results of toxicological and safety studies. This especially applies to preparations which contain for example a hitherto unknown excipient, or for preparations whose final composition (mixture of all active and inactive ingredients) potentially causes systemic absorption. It is also necessary to take into consideration the fact that the illness itself may also influence absorption.

Table 4. Prescription of antiglaucomatous drugs in the Slovak Republic in 2012

	Number of packages (thousand items)	Inter-year growth (%)	Sale (thousand CZK)	Inter-year difference
Cosopt	143.0	+7.8	1 385.5	-4.1
Azopt	102.9	+18.2	755.0	+16.6
Xalatan	102.6	-7.8	908.6	-9.3
Trusopt	62.1	+6	353.7	-1.4
Brimonal	52.2	+6.5	445.9	+6
Xalacom	48.4	0	575.3	-1.6
Lumigan	42.9	+3.9	163.5	+0.8
Unilat	41.4	+56.4	265.7	+33
Travatan	38.4	-16	407.5	-18.7
Combigan	32.0	0	320.1	0
Duotrav	22.7	0	280.8	-4.1
Ganfort	22.2	+18.0	285.1	+16.5
Pilocarpine	20.0	+11.1	37.0	+11.8

Table 5. Daily dose of benzalkonium chloride (BAC) in glaucoma therapy with beta-blockers and alpha-mimetics (ug)

BETA-BLOCKERS	
Timo COMOD	0
Arutimol	2.6
Vistagan	2.8
Timolol-POS	3.0
Arteoptic	3.7
Betoptic S	4.8
Timoptol MSD	6.3
Betoptic	10.0
ALPHA-MIMETICS	
Alphagan	3.5
Luxfen	3.5
Aruclonin	7.1

Therapeutic equivalence of the referential and tested medicinal products can be demonstrated by two methods. The first is "pharmaceutical equivalence", which is the fundamental resemblance of the two products from the perspective of quality. The referential and tested products must have the same qualitative and quantitative composition. Small differences are acceptable on condition that they are justified in detail by the applicant, and that they are expected to have no influence on the safety and efficacy of the product. An example is the different quantity of buffers for the purpose of attaining the optimum pH of the preparation. The type and quantity of impurities in the product are also evaluated. Impurities are specified in the European codex and the Czech codex. In the tested preparation, the stated values must not exceed the permitted limits.

For the purpose of demonstrating pharmaceutical equivalence, the applicant conducts a range of comparative in vitro tests, for example determination of osmolarity, pH, viscosity, drop size, i.e. all the parameters which may influence the size of the dose and consequently efficacy and safety. The results of these tests may differ only minimally between the referential and tested products.

The fundamental resemblance of two eye preparations may also be demonstrated by a clinical study of therapeutic equivalence. These studies are similar to phase III clinical studies, and with regard

to their time and financial demands are conducted less frequently. The applicant usually conducts the trials if he/she is unable to demonstrate the pharmaceutical equivalence of the two products, i.e. if the composition and physicochemical properties of the tested and referential products differ substantially.

Upon completing the marketing authorization proceedings, the medicinal product may be introduced onto the market and its use in clinical practice may be commenced. It thereby enters the post-marketing phase, in which its presence on the market, quality and the occurrence of undesirable effects are monitored.

The presence of the product on the market is monitored by means of reporting of deliveries by distributors every three months. If a medicinal product is not introduced onto the market within three years of the issuing of the decision on marketing authorization, the marketing authorization expires and the product can no longer be introduced onto the market. Before the cancellation of the marketing authorization due to absence on the market, it is always assessed as to whether the medicinal product can be substituted in clinical practice by another product, and whether it is essential for the protection of public health. If both of these conditions are met, the medicinal product is granted an "exception", and remains on the market. Unless both of these conditions are met simultaneously, the decision on the marketing authorization is cancelled and the drug can no longer be introduced onto the market.

At present, SÚKL frequently encounters the situation in which deliveries of a medicinal product are interrupted for various reasons. Interruption of deliveries may be caused for example by a fault in manufacture (including errors in the summary of product characteristics, container or package information leaflet), or more often the inability of the contractual manufacturing organisations and suppliers of active ingredients and excipients to cover the demand. In such cases, pursuant to Act no. 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts, the holder is obliged to notify SÚKL of the interruption, including the date of interruption and the date of resuming of deliveries. Interruption of deliveries should be reported at least two months in advance, in order to ensure that SÚKL has sufficient time to assess whether the product can be substituted by another in the clinical practice and if applicable to take measures in order to ensure fluency of deliveries (for example permission of import of a foreign language batch or permission of import of a batch which is not bound to the same documentation which SÚKL approved in the marketing authorization proceedings).

The SÚKL tools for preventing shortages of medicinal products are relatively limited, and it often depends on the ability of the holder to find a suitable batch of the product and import it to the Czech Republic.

Another aspect of post-marketing surveillance of medicinal products is monitoring of quality and compliance with the marketing authorization documentation and the information stated in the summary of product characteristics. Initiatives relating to quality defects are received from patients, doctors, marketing authorization holders, distributors, manufacturers or other regulatory authorities. In 2012 SÚKL received an initiative on the non-compliance of the data on the number of drops in a millilitre of the preparation stated in the SPC with the actual content. On the basis of this reporting SÚKL launched a systematic control of eye preparations with the aim of verifying whether the number of drops per millilitre actually corresponded to the quantity stated in the summary of data about the preparation. Of 58 tested samples, 89% complied with the specifications. The holders of marketing authorization of those preparations in which a discrepancy between the declared and actual amount of drops was found must correct this matter in the summary of product characteristics and the package information leaflet. An alternative solution is recall from the market due to quality defect.

Reporting of adverse drug reactions following the registration of a medicinal preparation is an integral part of the life cycle of a medicinal product, and brings very valuable information about the characteristics of the product, which were not detected during the course of the clinical trials. Healthcare employees have a legal obligation to report all suspected adverse drug reactions to SÚKL (Table 14). SÚKL also accepts reports of suspicion of adverse drug reactions from patients. A further source of information about undesirable effects after the introduction of a medicinal preparation onto the market is individual cases published in the professional literature, pharmacoepidemiological studies or post-marketing clinical trials. SÚKL processes all reports and subsequently submits them to the European database of adverse drug reactions Eudravigilance and the World Health Organisation (WHO). The causal connection between the use of a drug and an adverse drug reaction thereof is assessed by experts in the field of pharmacovigilance as improbable, possible, probable or certain. If there is more than one report, a pharmacovigilance signal is generated. A further verification of the pharmacovigilance signal demonstrates whether a new adverse drug reaction has been discovered. If there is sufficient data, the frequency of occurrence is determined and the information is added to the summary of product characteristics and the package information leaflet. The frequency or seriousness of an already known adverse drug reaction may also change on the basis of an assessment of the signal, or marketing authorization of the drug may be cancelled. In certain cases, the adverse drug reactions identified after the introduction of a medicinal product onto the market are so significant that the risks outweigh the benefits of treatment. In such a case marketing authorization is cancelled. Information about undesirable effects is published on the websites of SÚKL and EMA.

Healthcare employees should report adverse drug reactions which are life-threatening, cause death, require hospitalisation, result in permanent or significant damage to health or limitation of abilities, or which are manifested as a congenital anomaly or congenital defect in offspring. Unexpected adverse drug reactions the nature, seriousness or consequences of which are in conflict with the information stated in the summary of product characteristics are also reported. Adverse drug reactions which bring new scientific knowledge and are of interest from a clinical perspective should also be reported. Specifically in the case of eye preparations, the most important are cases in which the adverse drug reactions are caused by systemic absorption of the active ingredient. SÚKL may contact the reporting person in the case that it is necessary to supplement or clarify any matter, but does not communicate information about the reporting person to third parties.

Off-label use of a medicinal product is such use which is not in accordance with the information stated in the summary of product characteristics. This may be use on another population of patients (for example paediatric), higher or lower than approved dose or way of administration, use of a certain property of the drug in non-medical cases (e.g. use of the Lumigan product for supporting growth of eyelashes) etc. Off-label use is not illegal, but Act no. 378/2007 Coll., on Pharmaceuticals in Section 8 specifies the conditions under which a medicinal pro-

duct may be used off-label if there is no other medicinal product with approved use and if such use is sufficiently scientifically justified. The attending physician is obliged to inform the patient in advance that this represents off-label use. The operator of the healthcare facility is liable for any damage to health.

A further significant chapter from the perspective of the doctor and patient is the availability of drugs.

Health insurance companies in Germany pay pharmacists bonuses for savings made by purchasing cheaper pharmaceuticals – for example in the Czech Republic. Due to their low price in the Czech Republic, manufacturers are even withdrawing certain drugs from distribution. At the same time, however, there is a functioning mechanism by which the state ensures that a certain drug is not more expensive in the Czech Republic than elsewhere in Europe. From this situation there ensues a significant fact – in official overviews of costs for drugs and in practice, a significant feature of the present situation is the phenomenon of "re-export". Due to their low price, certain pharmaceuticals are purchased in the Czech Republic and then exported abroad. This drainage abroad currently relates to more than 300 pharmaceuticals. In some cases this situation particularly does not matter yet, but in a range of cases it does. The result of this situation is that certain drugs are not available for our patients. The problem of poor availability on our market has arisen in the case of the following drugs: Humalog, Clexan, Berudual, Remicade, Mycardis, Prestance, Asmanex, drugs for HIV positive patients etc.

Some companies address this situation via the method of direct distribution to certain pharmacies, in which the drug is supplied for a particular patient. This situation is naturally far from ideal, in addition for the company it involves further costs. From the proposal for the prohibition of re-export, which would be a solution to the problem, there remained a change approved by the legislators in February 2013: distributors shall be obliged to announce what they are exporting. Restriction of export could be understood as an "infringement of free trade", and so the problem has been shifted from the professional level to the political arena. It does not concern an insignificant amount of money – if re-export represents an estimated 20% of the market, then this concerns 10 billion CZK. In Slovakia a prohibition of re-export is possible, even if it is allegedly in conflict with the European "free market" legislation. The risk is only of a "reprimand".

Prescription and indication restrictions

In the Czech Republic a range of regulatory measures are applied, reducing the costs for healthcare, which also include the measure that some drugs shall be reimbursed from public health insurance only if they are prescribed by certain specialists or only for patients with a certain condition of health (6). Over a period of several years, the number of medicinal products which are restricted in this manner has more than doubled. In the EU at least six countries restrict the prescription of drugs for diagnostic procedures (Sweden), though restriction to concrete medical specialization in a certain form was found only in Austria and the Netherlands. In contrast with the Czech Republic, only highly specialised pharmaceuticals (new biological drugs, new oncological drugs) are restricted in this manner.

Prescription and indication restrictions for medicinal preparations rank amongst the "conditions of reimbursement" stipulated by SÚKL, together with the amount of reimbursement within the framework of administrative proceedings. A prescription restriction means that a medicinal preparation is prescribed only by a doctor with the relevant specialism (symbol E), or may be prescribed by another doctor but only on the basis of a written approval of a doctor with the relevant specialism (symbol L). Symbol P means that SÚKL has defined the indications in which the medicinal prescription is paid for from public health insurance.

Before 2008, these restrictions were discussed within the framework of the categorisation commission with representatives of professional societies, i.e. with doctors who are capable of assessing the expediency of such measures. Now that the only opponents of SÚKL are health insurance companies and representatives of pharmaceuticals companies, it is no surprise that the views of clinical doctors are not being heard in some cases.

From the above it is evident that prescription and indication restrictions are sometimes rather the act of lawyers than informed regulators who are sufficiently familiarised with the issue of pharmaceuticals in clinical practice. As a result, the savings declared on paper may in reality become losses. This is contributed to by further bureaucratic measures. Previously it was the case that a doctor must have the relevant specialism – attestation. Now the relevant specialism is taken as the specialty which the doctor (or workplace of the healthcare facility) has stated in the contract with the health insurance company. In practical terms such a restriction is stipulated for each new pharmaceutical (with the exception of generics), but only few drugs lose the restriction.

There is no other country in which a doctor could automatically be fined for breaching a restriction of prescription to the doctor's specialty. Advanced countries prioritize systematic support for targeted pharmacotherapy, regular analyses of prescription and the performance of audits where there is suspicion of suboptimal care, not only with regard to wastage but also from the perspective of the quality of healthcare.

Information on reimbursement, prices and the amount of the applicable supplementary payment for medicinal products

A resource for ophthalmologists in deciding on the treatment of patients with glaucoma may be the portal of the Ministry of Health of the Czech Republic. In the "Pharmaceuticals" section it is possible to find a range of useful data. We present a selection of the monitored terms and also the most interesting data for certain drugs which could serve for better orientation within this problem for doctors and patients. The "maximum reimbursement by the health insurance company" – the amount of payment for a medicinal preparation by health insurance companies from public health insurance – it projects in the costs of the healthcare facility. The "highest possible price in a pharmacy upon the dispensing of a prescription drug" – the medicinal product is subject / not subject to regulation by maximum price (price prescription of the Ministry of Health 1/2012/FAR of 12 December 2011). This ensues from the maximum price stipulated by SÚKL/manufacturer, increased by the maximum commercial surcharge and VAT. The "highest possible supplementary payment by patient upon the dispensing of a medicinal preparation" is the difference between the highest possible price in the pharmacy and the maximum reimbursement by the health insurance company. The "average current price in a pharmacy" corresponds to the average

Table 6. Miotics – maximum reimbursement by health insurance company, average supplementary payment by patient

	MRHIC (CZK)	ASP (CZK)
Fotil forte	218.00	8.92
Fotil	156.71	60.69
Pilogel	60.45	159.14

Table 7. Beta-blockers – maximum reimbursement by health insurance company, average current supplementary payment by patient

	MRHIC (CZK)	ASP (CZK)
Betoptic	94.50	22.95
Betoptic S	60.13	49.84
Vistagan	57.27	41.84
Carteol III	192.43	88.05
Arteoptic III	192.43	96.42
Timolol POS 0.25 III	85.91	62.95
Timolol POS 0.5 III	171.81	16.37

Table 8. Adrenergic agonists – brimonidine – maximum reimbursement by health insurance company, average current supplementary payment by patient

	MRHIC (CZK)	ASP (CZK)
Alphagan	60.45	253.25
Luxfen	81.25	69.62

Table 9. Carboanhydrase inhibitors – maximum reimbursement by health insurance company, average current supplementary payment by patient

	MRHIC (CZK)	ASP (CZK)
Brinzolamide 1%		
Azopt	265.29	26.28
Azopt III	801.17	55.49
Dorzolamide 2%		
Trusopt	247.58	0
Oftidor	249.25	0

Table 10. Prostaglandin analogues, prostamides – maximum reimbursement by health insurance company, average current supplementary payment by patient

	MRHIC (CZK)	ASP (CZK)
Xalatan III	913.50	0
Travatan III	913.50	60.32
Lumigan III	913.50	279.64
Taflotan 90x 0.3 ml	978.74	295.74
Taflotan 30x 0.3 ml	326.25	142.37

Table 11. Fixed combinations – maximum reimbursement by health insurance company, average current supplementary payment by patient

	MRHIC (CZK)	ASP (CZK)
Xalacom III	1528.36	0
Xalacom I		0
Glucotima I	346.44	0
Duotrav III	1528.36	0
Duotrav I		77.42
Ganfort III	1547.21	0
Ganfort I		0
Combigan	111.25	201.53
Cosopt III	790.64	298.80
Dorzogen Combi III	800.45	0
Dozotima I	263.55	0
Azarga III	1089.72	183.87
Azarga I	369.24	99.48

price on the market in the Czech Republic in the elapsed period – this may differ in individual pharmacies. It represents referential data, based on the prices in distribution increased by the margin and VAT as of 1 January 2013, updated always after the 21st of the following calendar month. The "amount of the supplementary payment calculated within the annual limit" is calculated up to the limit of CZK 5000 (CZK 2500 up to 18 years and over 65 years).
The "average current supplementary payment by patient" corresponds to the average supplementary payment on the market in the Czech Republic in the elapsed period. Supplementary payments may differ in individual pharmacies. It is precisely this indicator that may be highly useful in the decision of the patient or doctor on where to collect the prescribed medication (Tables 6-11).
MRHIC – maximum reimbursement by health insurance company
ASP – average current supplementary payment by patient.
Commentary on most interesting data:
Surprisingly, from the perspective of the supplementary payment for the patient, in the case of miotics the most advantageous is the triple package of the more effective Fotil forte (Table 6). Beta-blockers in the treatment of primary open angle glaucoma are a popular variant. In the current overview of supplementary payments for patients, the most financially advantageous is the triple package of 0.5% Timolol POS (Table 7). The multiple difference in the supplementary payment for the patient in the groups of adrenergic agonists is evident from Table 8. Glaucoma therapy with local carboanhydrase inhibitors is cheap, nevertheless here we still find financial differences in the supplementary payment for the patient (Table 9). The carboanhydrase inhibitor for general administration is also with a supplementary payment – Diluran – ASP CZK 13.03. Prostaglandin analogues are a very attractive group for patients with regard to the supplementary payment. We can observe how large pharmaceutical companies react to the presence of generics on the market also in the amount of the average current supplementary payment (Table 10). The situation of the ASP for fixed combinations in glaucoma therapy also helps orientation between the particular drugs (Table 11).

8. Glaucoma surgery – costs and comparison with conservative therapy

The point evaluation of glaucoma surgery (Table12) provides illustrative evidence of the absolutely insufficient appreciation of the professional work of ophthalmic surgeons. Even if the value of one point was guaranteed at CZK 1.00, we are within the range of price relations for glaucoma surgery

Table 12. Procedures tariff – glaucoma operations codes

	Time – points
75339 trabeculectomy	40-1568
75337 iridectomy	20-1286
75341 cyclocryotherapy	15-110
75335 laser procedure in angle of anterior chamber of eye	20-320
Add use of surgical microscope	

Table 13. Ocular glaucoma implants – ZUM /= extra charged material/

		Max. payment	distributor
ExPress	0163638	CZK 12 778.36	Novartis, Alcon
T flux	0163294	CZK 12 338.950	Zeiss
Silicon 44	0163309	CZK 5 648.16	
Healaflow	0192613	CZK 6 156.00	Anteis, Videris
Ahmed valve AGVB4	0163631	CZK 2 955.71	New World Medical Inc., Videris
Ahmed valve AGFFX4	0163629 0163628 FP7, FP8	CZK 3 703.96 CZK 9 414.33	Ahmed paediatric
Ahmed paediatric	0163630 S2, S3	CZK 10 180.20	
Ologen	0161501	CZK 6 199.00	
Glaucolight 3x		CZK 32 794.00	Spirit Medical

Table 14. Report of suspect adverse drug reaction

farmakovigilance
BEZPEČNÁ LÉČIVA

HLÁŠENÍ PODEZŘENÍ
na nežádoucí účinek léčiva

SÚKL
Státní ústav pro kontrolu léčiv

1. Informace o hlásícím

Razítko:

Jméno a adresa osoby podávající hlášení
(důvěrná informace - SÚKL nesděluje jiným subjektům)

Datum tohoto hlášení (den / měsíc / rok 2 0)

Hlášeno také držiteli ☐ ANO ☐ NE
Zdravotnický pracovník ☐ ANO ☐ NE

2. Informace o pacientovi a nežádoucím účinku

INFORMACE O PACIENTOVI

Iniciály pacienta

Pohlaví ☐ muž ☐ žena

Datum narození (den / měsíc / rok)

Věk

Nástup reakce (den / měsíc / rok 2 0)

VYZNAČTE VŠE, CO ODPOVÍDÁ ZACHYCENÉ REAKCI

☐ Pacient zemřel (den / měsíc / rok 2 0)
☐ Došlo k ohrožení života
☐ Nežádoucí účinek byl důvodem hospitalizace nebo jejího prodloužení
☐ Vznikly trvalé následky
☐ Vrozená vada / perinatální poškození
☐ Jiná lékařsky významná událost

Popis nežádoucího/cích účinku/ů

Výsledky souvisejících vyšetření (včetně dat provedení)

Další podstatné anamnestické údaje

3. Informace o léčivu / léčivech

Lék podezřelý z vyvolání nežádoucího účinku — Číslo šarže:

Obchodní název	síla	dávkování	podávání od / do (den měsíc rok / den měsíc rok)	způsob/y podávání	indikace pro podání
			/		
			/		

Souběžná léčiva (včetně léků podávaných až 3 měsíce před výskytem účinku)

Léčba nežádoucího účinku

Odezněla reakce po vysazení léčiva?
☐ ANO ☐ NE ☐ neaplikovatelné

Objevila se reakce znovu po opětovném nasazení léčiva?
☐ ANO ☐ NE ☐ neaplikovatelné

VEŠKERÉ ÚDAJE LZE ROZVÉST NA DALŠÍCH STRANÁCH ANEBO LZE PŘIPOJIT DALŠÍ RELEVANTNÍ DOKUMENTY (NAPŘ. VÝSLEDKY VYŠETŘENÍ, LÉKAŘSKÉ ZPRÁVY)

Vyplněné hlášení (i neúplné údaje) zašlete, na adresu:
SÚKL, Farmakovigilance, Šrobárova 48, Praha 10, 100 41, fax: 272 185 222, e-mail: farmakovigilance@sukl.cz

which do not even reach the value of a family's weekend shopping at a supermarket. An adequate situation would be possible after the introduction of the Euro, if point evaluation was retained. For health insurance companies, in the present situation it would be most advantageous to have surgery performed cheaply on all glaucoma patients – further costs in connection with demanding medicamentous treatment would be eliminated. The reality is naturally different, and is not the subject of this article.
In a certain group of patients it is possible to achieve compensation only with the use of glaucoma implants. We present a current overview and the price costs thereof (Table 13).

9. Conclusion

At present we are witnesses to substantial progress in the diagnosis and therapy of glaucoma. Patient awareness of this disease has fundamentally improved also thanks to the media, in particular the internet. A very varied assortment of pharmaceuticals is available for conservative therapy, as well as several new intervention procedures. In deciding on treatment, doctors are governed not only by the principles of good clinical practice and by their knowledge, but must also bear in mind a range of further related factors. The patient and doctor are within a specific environment in which both economic and legislative costs exert a considerable influence. For better orientation within this issue, an overview of the data and information relating to glaucoma therapy has been created in co-operation with pharmacologists and the state authority (SÚKL).

LITERATURE

1. Daull, P, Garriguie, J.S.: Preservative-free cationic nano emulsion of latanoprost. Ophthalmology Times Europe, Jan/Feb 2013: 8–10.
2. Doležal, T.: Od molekuly k dlouhodobé spokojenosti pacienta. Farmakoterapie, 2; 6, 2012: 4–6.
3. Herndon, L.W, Asrani, S.G., Williams, G. H. et al.: Paradoxial intraocular pressure elevation after combined therapy with latanoprost and bimatoprost. Arch Ophthalmol, 120; 2002: 847–849.
4. IMS Health – analytická společnost, Praha, Dataview 2010–2012.
5. Liang, H., Baudoin, P., Daull, P. et al: In vitro and in vivo evaluation of preservativefree cationic emulsion of latanoprost in cornal wound healing. Cornea, 31; 2012: 1319–1329.
6. Prokeš, M.: Prekripční a indikační omezení pro léky v České republice. Farmakoekonomika, 6; 2012: 2–6.
7. Výborný, P., Sejčková, L.: Antiglaukomatika – obsah konzervaãních látek a spolupráce pacienta v léčebném režimu. Čes a Slov Oftal, 62; 2006: 270–274.
8. Výborný, P., Dohnalová, P., Sičáková, S.: Antiglaukomatika v šíslech a tabulkách – trendy v preskripci. In Trendy soudobé oftalmologie, svazek 8, Ed. Rozsíval P., Praha, Galén 2012, 247–255.
9. Výborný, P., Fučík, M., Rozsíval, P.: Glaukom. In. Kuchynka P. et al. Oãní lékařství, Praha, Grada 2007, 596–607.