RATIONAL USE OF MEDICINES:

THE ROLE OF THE DRUG AND THERAPEUTICS COMMITTEE

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Over a number of years, the World Health Organization (WHO) has heavily promoted the concept of the rational use of medicines. WHO defined the rational use of medicines in 1985:

"Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community."

For professionals involved in providing healthcare this may seem obvious, however, it is apparent that medications are prescribed and supplied inappropriately in more than 50% of cases.[1] Not only does this impact on the care of the patient and management of their overall health, but can also be costly and waste valuable resources. Inappropriate antibiotic use, in addition, may lead to microbial resistance which can impact on the wider community. The implementation of a drug and therapeutics committee has been shown to be one of the most effective structures for supporting the rational use of medicines within hospitals.[2]

Within the UK there are a number of measures used to promote the rational use of medicines at both a national and local level. National guidelines developed by specialist bodies such as the British Thoracic Society or the National Institute for Clinical Excellence (NICE) help to define specific treatments which are safe and effective for the management of specific disease states, and in addition, NICE guidance will often indicate whether a drug or device is considered to be cost effective.

A DTC can have a significant impact in applying national guidance to the local community, including the hospital in which it operates, and any affiliated primary care prescribers. Where national guidance does not exist, the DTC is often involved in developing and promoting local guidance based on individual assessments of drug safety, efficacy and cost implications, and this is usually done in consultation with local specialists.

In addition to developing or adapting treatment guidelines DTC's in the UK take on a number of other roles with respect to rational use of medicines, including the following:[2]

- **Evaluating and selecting drugs for addition to the formulary list** (or essential medicines list) – an individual drug review should include information on the safety, efficacy, cost, and relevant practicalities of prescribing.
- **Assessing current medicines use in order to identify problems** – this may include overuse, use in inappropriate patients, or medication supply problems. After adding a drug to the local formulary, this would include follow up of the drug and how extensively it is used, and also of the cost to make sure that assessments of budget impact have not changed significantly.
- **Developing policies on the prescribing, supply and administration of medicines**, either generalised (such as a medicines code of practice) or specific to a particular drug/disease state.
- **Conducting interventions to improve drug use** – may involve restrictions to prescribing, general guidance and advice, drug use monitoring etc.
- **Managing adverse drug reactions and medication errors** – discussion of adverse events or errors and their potential causes can help to identify monitoring requirements which may improve the safety of drug use, and serious or commonly occurring errors which can then be addressed.
- **Providing and endorsing advice on all aspects of drug management**
- **Circulating information to all staff** regarding drug use issues, policies and local decisions.

Because there is a wide range of expertise required to undertake these functions, it is recommended that the DTC members be made up of multidisciplinary team members such as doctors, pharmacists, nursing staff, hospital managers, and any other professionals who are deemed relevant for the functions of the committee. I have included a list of the members at my own hospital trust as an example below:

Members of the Committee at Barnsley Hospital (small general hospital):

- Medical director plus 4 medical consultants
- Chief pharmacist plus 3 senior pharmacists (to include medicines information pharmacist)
- Deputy chief nurse plus lead nurse from all clinical areas (8 areas)
- Hospital executive director
- 2 members of the hospital risk management team
- 2 members of the hospital audit team
- Administrative staff (for taking and distributing minutes/agenda etc.)

The committee undertakes a number of regular audits around the use and handling of medicines within the trust, hence why members of the audit team regularly attend, and the risk management team help to manage decisions and interventions around drug errors. At first glance there may seem to be a large number of doctors, pharmacists and nurses on the committee, but the reason for this is so that if some members cannot attend due to other commitments, there should always be at least one representative from each and decisions can still be made.

A large amount of the work undertaken by the committee is by, or in conjunction with, the pharmacist members. The pharmacists would usually have extensive or sole input into writing the drug reviews for addition of medicines to the formulary, writing local guidelines or adjusting national guidelines to suit local practices, and advising on all other medicines related matters including the use of unlicensed medicines. Each committee member is responsible for feedback of the committee's decisions to their relevant work areas.

If a DTC covers prescribing in primary care in addition to a hospital trust, then the membership should reflect this by including relevant medics, pharmacists and other healthcare professionals within the community.

It is important that the DTC and its function is endorsed and supported by the hospital management to make sure that members are given time to undertake the necessary work and attend meetings. It is also paramount in adding weight to any guidance or recommendations made by the committee.

References:

1. WHO factsheet 338 Rational use of Medicines (May 2010). Accessed online via www.who.int/mediacentre/factsheets
2. Holloway K (ed.) and Green T. Drug and Therapeutics Committee: A Practical Guide 2003. *WHO department of essential drugs and medicines policy in collaboration with Management Sciences for Health (Center for Pharmaceutical Management) USA.* Accessed online via www.apps.who.int.medicinedocs

New Drug Request Summary for Barnsley APC
Prucalopride (Resolor®▼)

Date Completed: March 2012

Introduction

Prucalopride is a highly selective 5-HT_4 receptor antagonist which stimulates the motility of the colon. It is licensed at a dose of 2mg daily (initially 1mg daily in the elderly) for the symptomatic treatment of chronic constipation in women whom laxatives fail to provide adequate relief.

Prucalopride has a similar mode of action to cisapride, which was discontinued a number of years ago due to risk of QT prolongation, amongst other prominent adverse effects.

Treatment should be discontinued after 4 weeks if there is no response.

Efficacy

Evidence from the studies suggests that prucalopride can improve bowel function in a significant number of patients who are resistant to the use of laxatives in chronic constipation. A number of patients, however, did not respond in the trials and would require further intervention.

Trial Name and design	Duration	Details	Outcomes
Camilleri M et al. **PRU-USA-11** N = 620	12 weeks	Multicentre randomised, placebo controlled parallel group study. Patients with chronic constipation, defined as ≤ 2 spontaneous, complete bowel movements per week for a minimum of 6 months prior to the screening visit. Subjects were randomised to receive prucalopride 2mg daily, prucalopride 4mg daily or placebo. Laxative use in general was disallowed. Rescue bisacodyl up to 15mg was allowed ONLY if patients did not have a bowel movement for 3 or more consecutive days during the trial, followed by an enema if this was not effective. Rescue therapy was not allowed within the 48 hours periods before and after the first dose of study drug.	Primary endpoint was the proportion of patients having 3 or more spontaneous, complete bowel movements per week, averaged over the 12 week study period. This occurred in 30.9% of patients taking prucalopride 2mg, 28.4% of patients taking prucalopride 4mg and 12.0% of patients taking placebo. (**NNT 5.3** patients for 12 weeks, prucalopride 2mg daily vs placebo). Secondary endpoints included the time to first spontaneous bowel movement, use of rescue medication and also involved use of diaries and questionnaires to elicit subjective opinions from patients. Median number of days to first spontaneous bowel movement were 1.3 for prucalopride 2mg, 1.0 for prucalopride 4mg, and 12.6 for placebo. Mean change in the use of rescue laxatives (number of bisacodyl tablets per week) from baseline was -1.0 (53%) for prucalopride 2mg, -0.8 (44%) for prucalopride 4mg and -0.1 (5%) for placebo. Patient-rated efficacy of treatment as effective or extremely effective at week 12 was 33.3% for prucalopride 2mg, 37.7% for prucalopride 4mg and 17.0% for placebo.

Tack J et al. **PRU-INT-6** N = 713	12 weeks	Multicentre randomised, placebo controlled parallel group study. Patients with chronic constipation, defined as ≤ 2 spontaneous, complete bowel movements per week for a minimum of 6 months prior to the screening visit. Subjects were randomised to receive prucalopride 2mg daily, prucalopride 4mg daily or placebo. Laxative use in general was disallowed. Rescue bisacodyl up to 15mg was allowed ONLY if patients did not have a bowel movement for 3 or more consecutive days during the trial, followed by an enema if this was not effective. Rescue therapy was not allowed within the 48 hours periods before and after the first dose of study drug.	Primary endpoint was the proportion of patients having 3 or more spontaneous, complete bowel movements per week, averaged over the 12 week study period. This occurred in 19.5% of patients taking prucalopride 2mg, 23.6% of patients taking prucalopride 4mg and 9.6% of patients taking placebo. (**NNT 10** patients for 12 weeks, prucalopride 2mg vs placebo). The key secondary endpoint was the proportion of patients having an increase of one or more spontaneous complete bowel movement per week. This occurred in 38.1% of patients taking prucalopride 2mg, 44.1% of patients taking prucalopride 4mg, and 20.9% of patients taking placebo. Median number of days to first spontaneous bowel movement were 4.7 for prucalopride 2mg, 2.1 for prucalopride 4mg, and 20.5 for placebo. Mean change in the use of rescue laxatives (number of days per week) from baseline was -0.4 (50%) for prucalopride 2mg, -0.3 (38%) for prucalopride 4mg and -0.2 (20%) for placebo. Patient-rated efficacy of treatment as effective or extremely effective at week 12 was 34.6% for prucalopride 2mg, 36.1% for prucalopride 4mg and 18.7% for placebo.
Quigley E M et al. **PRU-USA-13** N= 641	12 weeks	Multicentre randomised, placebo controlled parallel group study. Patients with chronic constipation, defined as ≤ 2 spontaneous, complete bowel movements per week for a minimum of 6 months prior to the screening visit. Subjects were randomised to receive prucalopride 2mg daily, prucalopride 4mg daily or placebo. Laxative use in general was disallowed. Rescue bisacodyl up to 15mg was allowed ONLY if patients did not have a bowel movement for 3 or more consecutive days during the trial, followed by an enema if this was not effective. Rescue therapy was not allowed within the 48 hours periods before and after the first dose of study drug.	Primary endpoint was the proportion of patients having 3 or more spontaneous, complete bowel movements per week, averaged over the 12 week study period. This occurred in 23.9% of patients taking prucalopride 2mg, 23.5% of patients taking prucalopride 4mg and 12.1% of patients taking placebo. (**NNT 8.5** patients for 12 weeks, prucalopride 2mg vs placebo). The key secondary endpoint was the proportion of patients having an increase of one or more spontaneous complete bowel movement per week. This occurred in 42.6% of patients taking prucalopride 2mg, 46.6% of patients taking prucalopride 4mg, and 27.5% of patients taking placebo. Median number of days to first spontaneous bowel movement were 2.3 for prucalopride 2mg, 1.9 for prucalopride 4mg, and 13.0 for placebo. Mean change in the use of rescue laxatives (number of bisacodyl tablets per week) from baseline was -0.7 (33%) for prucalopride 2mg, -1.0 (45%) for prucalopride 4mg and -0.1 (5%) for placebo.

Mueller-Lissner SA et al. **PRU-INT-12** N=	4 weeks	As for PRU-INT-6, PRU-USA-11 and PRU-USA-13 but only in patients aged ≥ 65 years. Patients were randomised to receive 1mg daily, 2mg daily or 4mg daily of prucalopride, or placebo. Laxative use in general was disallowed. Rescue bisacodyl up to 15mg was allowed ONLY if patients did not have a bowel movement for 3 or more consecutive days during the trial, followed by an enema if this was not effective. Rescue therapy was not allowed within the 48 hours periods before and after the first dose of study drug.	Primary endpoint was the proportion of patients having 3 or more spontaneous, complete bowel movements per week, averaged over the 4 week study period. This occurred in 39.5% of patients taking prucalopride 1mg , 32.0% of patients taking prucalopride 2mg, 31.6% of patients taking prucalopride 4mg and 20.0% of patients taking placebo. This difference was not statistically significant. The key secondary endpoint was the proportion of patients having an increase of one or more spontaneous complete bowel movement per week. This occurred in 61.1% of patients taking prucalopride 1mg, 56.9% of patients taking prucalopride 2mg, 50.7% of patients taking prucalopride 4mg, and 33.8% of patients taking placebo.
Camilleri M et al. N = 1775	24 months	Open label long term follow up study of the above three studies. Patients initially received prucalopride 2mg daily for 7 days, after which the dose could be self titrated up to a maximum of 4mg daily. Mean daily dose was 2.6mg daily.	The primary and secondary endpoints from the above studies were sustained throughout the long term follow up period.

Safety

The most commonly reported adverse effects within the trials included headache, nausea, diarrhoea, abdominal pain, abdominal distension, vomiting, dizziness and flatulence, and with the exception of abdominal pain these tended to be more prevalent in the prucalopride groups than in the placebo groups, as listed in the following table:

In pooled data for the three main trials, the majority of events were mild to moderate and were transient, although at least one severe event was reported by 18.7% for prucalopride 2mg, 21.2% for prucalopride 4mg, and 14.7% for placebo. At least one serious, non-fatal adverse event was reported by 2.0% of prucalopride 2mg, 2.9% with prucalopride 4mg, and 2.7% with placebo.

Adverse events resulted in drug discontinuation in 5.9% of patients taking prucalopride 2mg, 9.7% with prucalopride 4mg, and 3.6% with placebo.

There were no significant difference between the three treatment groups with respect to BP, heart rate, ECG monitoring, Haematology parameters, clinical chemistry parameters and urinalysis. None of these parameters changed to a clinically relevant extent over time in any of the studies.

The pooled data was specifically analysed to look at the effects of prucalopride on QT interval, and showed minimal significant changes in either the prucalopride 2mg, prucalopride 4mg or placebo groups. Among patients with a normal baseline QTc, prolonged QTc of 450 – 480ms were seen in 2.5% of prucalopride 2mg patients, and 3.5% of prucalopride 4mg patients, and 3.5% of placebo patients. Prolonged Qtc of 480 – 500ms were seen in 0.5% of prucalopride 2mg, 0% of prucalopride 4mg and 0% of placebo patients, and QTc of >500ms were seen in 0% of prucalopride 2mg, 0.2% of prucalopride 4mg and 0% of placebo patients.

Precautions for use

Prucalopride is contraindicated in patients with renal impairment requiring dialysis, and in Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease, and ulcerative colitis and toxic megacolon/megarectum.

Renal excretion is the main route of elimination of prucalopride and a dose of 1 mg is recommended in subjects with severe renal impairment.

Patients with severe and clinically unstable concomitant disease (e.g. liver, cardiovascular or lung disease, neurological or psychiatric disorders, cancer or AIDS and other endocrine disorders) have not been studied. Caution should be exercised when prescribing prucalopride to patients with these conditions. In particular it's recommended that prucalopride should be used with caution in patients with a history of arrhythmias or ischaemic cardiovascular disease.

In case of severe diarrhoea, the efficacy of oral contraceptives may be reduced and the use of an additional contraceptive method is recommended to prevent possible failure of oral contraception.

It is unlikely that hepatic impairment will affect prucalopride metabolism and exposure in man to a clinically relevant extent. No data are available in patients with mild, moderate or severe hepatic impairment, and therefore a lower dose is recommended for patients with severe hepatic impairment.

Prucalopride is not expected to alter the pharmacokinetics of drugs metabolised by the cytochrome P450 system, and in-vitro data suggest there is a low potential for drug-drug interactions. No clinically relevant interactions were seen between prucalopride and ketoconazole, warfarin, digoxin, alcohol, paroxetine, erythromycin, probenecid or cimetidine.

Other Options

Alternative treatments for chronic unresponsive constipation would include methylnaltrexone (for opioid induced constipation – also non-formulary), sacral nerve stimulation, behavioural therapy or surgery.

Cost

Prucalopride 2mg daily for 4 weeks will cost £59.52 (ex. VAT), which equates to £774 per patient per year if treatment were to be continuous.

Other NHS Reviews

NICE recommends prucalopride as a treatment option for some women with chronic constipation in whom laxatives have not provided adequate relief. The guidance recommends that prucalopride1 should only be considered in women:

- who have tried at least two different types of laxatives from different classes (at the highest tolerated recommended doses) for at least six months, but have not had relief from constipation, and
- in whom invasive treatment is being considered.

The Scottish medicines consortium (SMC) did not recommend the use of prucalopride following a review done in June 2011, the opinion being that the manufacturer did not present a sufficiently robust clinical and economic analysis to gain acceptance. The licence holder has subsequently indicated their intention to resubmit.

Prucalopride is included in the NHS map of medicine for the management of chronic constipation which can be accessed via the following links:

http://healthguides.mapofmedicine.com/choices/map/constipation_in_adults_and_the_elderly1.html

http://healthguides.mapofmedicine.com/choices/map/constipation_in_adults_and_the_elderly2.html

Prucalopride is placed as a fourth line option after lifestyle and dietary changes, first line laxatives and second line laxatives, but before referral to secondary care.

Points to Consider

- Prucalopride treatment is substantially more expensive than the majority of laxatives, but would be a cheaper option than escalation to more invasive procedures such as surgery.
- The application for prucalopride is for an amber classification, however, the NHS map of medicines indicates its use in primary care before referral to secondary care.
- Prucalopride, unlike cisapride, seems to have minimal effects on cardiac function and QT interval.
- Currently it is only licensed for use in women.

References

1. Prucalopride manufacturer's information accessed via www.emc.medicines.org.uk
2. Camilleri M et al. A placebo controlled trial of prucalopride for severe chronic constipation. *NEJM 2008; 358 (22): pp 2344 - 54*
3. Tack J et al. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut 2009; 58: pp 357 - 65*
4. Quigley EM et al. Clinical trial:the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation – a 12 week, randomised, double-blind, placebo-controlled study. *Aliment Pharmacol Ther 2009; 29(3): pp315 - 28*
5. Mueller-Lissner SA et al. Randomised, double-blind, placebo-controlled trial to evaluate efficacy safety of prucalopride (Resolor) in elderly patients with chronic constipation – abstract only. *Gastroenterology 2008; 134(4, suppl. 1): ppA157*
6. Camilleri M et al. Long term follow up of safety and satisfaction with bowel function in response to oral prucalopride in patients with chronic constipation – abstract only. *Gastroenterology 2009; 136 (suppl 1): pp A31*
7. NICE guidance TA 211: prucalopride for chronic constipation in women. Accessed online via www.guidance.nice.org.uk
8. SMC submission number 653/10 for prucalopride 1mg and 2mg tablet (Resolor) accessed January 2012 via www.scottishmedicines.org.uk
9. NHS map of medicine accessed March 2012 via NHS Choices website on www.nhs.uk

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Administration of Iloprost infusion in Rheumatology patients

Iloprost is a prostaglandin analogue which causes peripheral vasodilation, and is used in the management of Raynaud's disease and vasculitic ulcers. It is administered as a continuous infusion for 6 hours every day, usually for 5 consecutive days but the treatment period may occasionally last up to 4 weeks. Iloprost infusion is not licensed in the UK and should only be prescribed by a Specialist familiar with its use. **Please make sure that patients are advised to omit calcium channel blocker treatment on the days when iloprost is to be given.**

Contraindications include pregnancy, breastfeeding, active peptic ulceration, recent severe trauma and intracranial haemorrhage. Use with caution in patients taking anticoagulant or antihypertensive medications.

Adverse effects commonly include hypotension, increased heart rate, flushing, nausea and vomiting and headache. Other reported effects include bradycardia, pallor, sweating, flu-like symptoms, anxiety, nervousness, tremor, hyperglycaemia, drowsiness and chest pain.

Prescribing Iloprost:
Iloprost infusion should be prescribed as 0.05mg in 25mls of sodium chloride 0.9%, and the initial infusion rate is based on the patient's weight (see table below). The infusion rate should start at the lowest rate (0.5 nanograms/kg/min).

Iloprost infusion rate (mls/hr):

Iloprost dose (nanograms/kg/min)	**Patient weight (kg)**												
	40	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**
0.5	0.6	0.7	0.8	0.8	0.9	1.0	1.1	1.1	1.2	1.3	1.3	1.4	1.5
1.0	1.2	1.3	1.5	1.6	1.8	2.0	2.1	2.2	2.4	2.5	2.7	2.8	3.0
1.5	1.8	2.0	2.2	2.5	2.7	2.9	3.2	3.4	3.6	3.8	4.0	4.3	4.5
2.0	2.4	2.7	3.0	3.3	3.6	3.9	4.2	4.5	4.8	5.1	5.4	5.7	6.0

For patients outside these weight parameters, use the following equation to calculate infusion rate:

Infusion rate (mls/hr) **=** weight (kg) **x** 0.03 **x** iloprost dose (nanograms/kg/min)

Administration and Monitoring:

Prior to starting the infusion consider premedication with paracetamol or cocodamol 8/500, and metoclopramide, to improve initial tolerability.

The infusion should be started at the lowest rate (0.5 nanograms/kg/min), and increased to higher infusion rates in a stepwise manner every 60 minutes (providing blood pressure and pulse allow) until the maximum rate is achieved. If a patient experiences side effects with a rate increase, paracetamol/cocodamol and metoclopramide can be administered (if the patient wasn't premedicated) and retry the current rate, or reduce the rate back down to the previously tolerated dose. The maximum tolerated rate should then be continued for the remainder of the 6 hour infusion.

If excessive hypotension occurs with the initial infusion rate of 0.5 nanograms/kg/min, stop the infusion for 30 minutes or until symptoms start to resolve and restart at half the initial rate, with a view to increasing again after 60 minutes if blood pressure and pulse allow, as above. If the patient doesn't tolerate this reduced dose, contact the prescribing Dr to discuss whether further dose reductions are appropriate or whether treatment should be discontinued.

Blood pressure and heart rate should be monitored every 30 minutes throughout the infusion period and 30 minutes after the infusion has been stopped.

For further information contact Medicines Information on ext. 2857, or the Prescriber.

References:

1. Martindale: The Complete Drug reference, accessed online at www.medicinescomplete.com

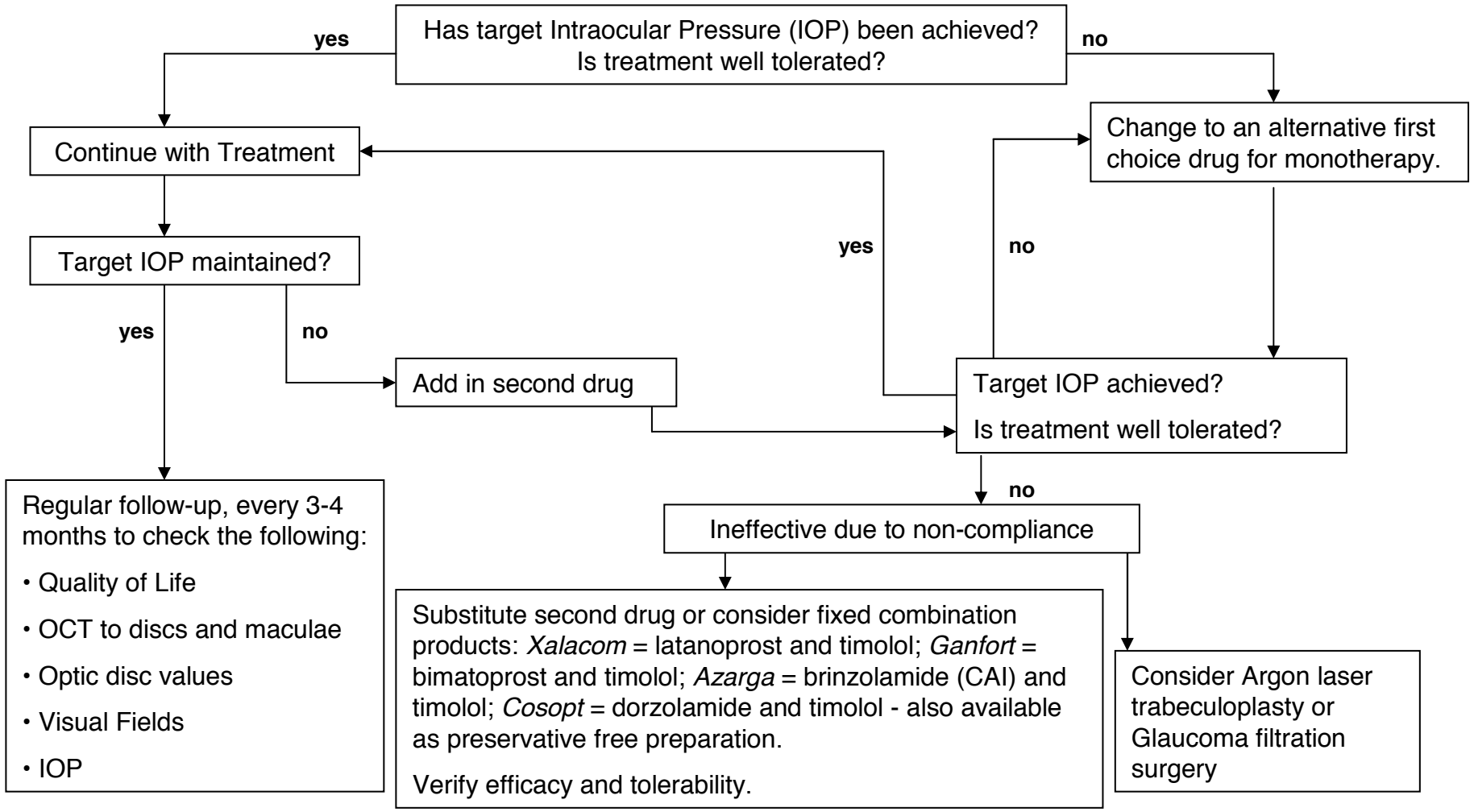
Dr V Bejarano, Consultant Rheumatologist
Gillian Smith, Medicines Information Pharmacist. December 2010

Algorithm for the Management of Glaucoma

Barnsley Hospital NHS
NHS Foundation Trust

First Choice Monotherapy (in order of preference)

1. Prostaglandin (Latanoprost or Travoprost; Tafluprost only if preservative free product required)
2. Beta-Blockers (Timolol, Betaxolol, Carteolol or Levobunolol)
3. Carbonic Anhydrase Inhibitors (CAI) (Dorzolamide – preserved and preservative free)
4. Alpha-Agonists (Brimonidine)



Adapted from European Glaucoma Society Terminology and Guidelines for Glaucoma 3rd Edition 2008.
Mr M J Hassan, Consultant Ophthalmologist. Gillian Smith, Lead Pharmacist. December 2010.