

NEWSLETTER

Supporting the Derbyshire Health Community

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JAPC Update

The Joint Area Prescribing Committee (JAPC) is a countywide group covering Derbyshire County PCT and Derby City PCT. It provides recommendations on drugs and medicines management issues.

RED drugs are those where prescribing responsibility lies with a hospital consultant or a specialist. AMBER drugs are those that are initiated within a hospital/specialist setting but are suitable for shared care with a GP under a shared care agreement. GREEN drugs are regarded as suitable for primary care prescribing. BROWN drugs are those that JAPC does not recommend for use, except in exceptional circumstances, due to lack of data on safety, effectiveness, and/or cost-effectiveness.

The most recent updates are in the table below; the full list is available at

<http://www.derbyshirecountypct.nhs.uk/clinical-guidelines-and-referral-guidelines.asp>

The guidelines, formulary chapters, newsletters, etc can now be found via this link.

Drug	Date considered	Decision
n-Acetylcysteine tabs	August 2009	AMBER
Degarelix injection	August 2009	BROWN
Fluticasone furoate nasal spray (Avamys)	August 2009	GREEN (after consultant initiation)
Liraglutide injection	August 2009	RED
Histrelin implant	August 2009	RED
Olapatadine eye drops	August 2009	GREEN (3 rd line use only)
Ondansetron tabs	July 2009	BROWN (moved from RED)
Optive eye drops	July 2009	GREEN

Update on safety of insulin glargine – part 2

Further to the article in last month's newsletter, the EMEA has issued a press release¹ that states:

"Following review of all available information on a possible relationship between insulin analogues, in particular insulin glargine, and the risk of cancer, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the available data does not provide a cause for concern and that changes to the prescribing advice are therefore not necessary."

It goes on to say that the evidence was inconclusive and did not allow a relationship between insulin glargine and cancer to be confirmed or excluded. Because of the limitations of the existing evidence, the Committee has requested the marketing authorisation holder, Sanofi-Aventis, to develop a strategy for generation of further research in this area.

An editorial points out that synthetic insulins differ from human insulins in both metabolic and cell-growth activities, which raises legitimate concerns about risk of malignancy². A letter to the Lancet³ states “Insulin is mitogenic; it promotes DNA synthesis and cell division. Insulin glargine is 6 to 8-fold more mitogenic than human insulin, and breast cancer cells proliferate in response to near-therapeutic concentrations of this analogue”.

The advice from the NPC⁴ is still valid:

“The effect of NICE guidance ought to be that the insulin analogues are not used routinely. However, the prescribing data for England shows that the uptake of insulin glargine and insulin detemir is now extensive. Based on the figures for the quarter to December 2008, there are about 1,200,000 items of insulin glargine prescribed each year, and 400,000 items of insulin detemir. This equates to approximately 40% of all intermediate/long acting insulin items. Whether or not a link between an increased risk of cancer and insulin glargine is established, given that the costs per QALY are so large for these analogue insulins, it may be prudent for prescribers and prescribing managers to now review the use of these drugs to see if their current use is indeed in line with NICE guidance.”

1. www.emea.europa.eu/humandocs/PDFs/EPAR/Lantus/47063209en.pdf
2. Lancet 2009; 374:511-13
3. Lancet 2009; 374:521
4. www.npci.org.uk/blog/?p=374

Travel and risk for VTE

A systematic review and meta-analysis of studies of travel and risk for venous thromboembolism (VTE) has been published¹. This reports that travel is associated with a nearly 3-fold higher risk for VTE, with a dose-response relationship of 18% higher risk for each 2-hour increase in travel duration.

The authors comment that the demonstration of a dose-response relationship suggests a causal nature to the observed relationship between travel and VTE. Among studies that evaluated air travel alone, the dose-response relationship seemed stronger (26% higher per 2 hours of travel). They add that the results should apply to general populations in Western countries.

These are of course increases in relative risk and absolute risk should guide decision making about prevention. One retrospective cohort study identified by the authors estimated the absolute risk for VTE to be 1 case in 4,600 airline flights. This study drew its sample from healthy employees of multinational organisations and the observed absolute risk may not be generalisable to all travellers, particularly those who may be at higher risk for VTE, such as older persons, pregnant women, or persons with a history of VTE.

Several RCTs have evaluated the effectiveness of lower-extremity compression stockings for prevention of travel-related DVT. These trials have generally reported them to be effective, at least for preventing DVT in the calf.

1. Ann Intern Med 2009; 151:180-90

Dose warfarin interact with oseltamivir or zanamivir?

During the current Swine Influenza (influenza A H1N1v) pandemic, a number of cases have been seen of a significantly increased International Normalised Ratio (INR) in people taking warfarin whilst they have been treated with oseltamivir. This has raised the question of whether there is a drug interaction between oseltamivir and warfarin. A UKMi Q& A tries to answer this¹.

Manufacturers' information and the standard drug interactions texts do not highlight any risk of a drug interaction between warfarin and oseltamivir or zanamivir. No published studies or case reports were identified in a search of standard databases.

Warfarin is susceptible to drug interactions via the following mechanisms:

- an effect on the absorption of warfarin
- the inhibition of intestinal bacterial production and absorption of vitamin K₂
- the inhibition of the absorption of vitamin K₁ present in food
- an alteration of the plasma protein binding of warfarin
- an alteration of the metabolism of warfarin by liver microsomes

It does not seem likely that either zanamivir or oseltamivir would interact with warfarin by one of these mechanisms. They are protein bound to only a relatively small extent and they are neither substrates, inducers or inhibitors of cytochrome P450 enzymes.

One of the key clinical features of the H1N1 virus currently prevalent is that it causes a sudden fever (a high body temperature of 38°C/100.4°F or above). It is known that acute febrile illness can lead to an increase in the effects of warfarin. This is thought to be due to an increased catabolism of clotting factors.

In 2006, the Canadian Adverse Drug Reactions Newsletter reported that 19 cases of increased INR in patients taking oseltamivir concurrently with warfarin were received between 1999 and 2005. The report includes the comment that "*Causality assessment of these cases is difficult because some of the reports presented conflicting or insufficient clinical information, and numerous factors (e.g. diet, medical conditions, fever) are known to influence a patient's response to anticoagulants*". It goes on to discuss the low potential for oseltamivir to interact with warfarin by currently understood mechanisms.

Summary

Whilst reports exist of increases in the INR of people taking warfarin and oseltamivir, the mechanism for a possible interaction has not been proposed. Whilst a specific interaction between warfarin and oseltamivir (or zanamivir) cannot be ruled out, it may be that the fever associated with swine flu is a more likely cause of these cases of raised INRs in people on warfarin.

The MHRA have set up a specific section of their website (<http://swineflu.mhra.gov.uk/>) for the public and professionals to report suspected side effects to particular medications administered during this time period to manage influenza.

1. [UKMI Q&A 280.1](#)

Neuraminidase inhibitors in children

A systematic review and meta-analysis of RCTs to assess the effects of oseltamivir and zanamivir in the treatment of children with seasonal influenza and prevention of transmission to children in households has been published¹.

The authors systematically searched the literature for randomised controlled trials evaluating neuraminidase inhibitors (oseltamivir, zanamivir) for the treatment or prophylaxis of confirmed or clinically suspected influenza in children ≤ 12 years in the community. Seven identified trials were of a sufficient quality and met the inclusion criteria – four were treatment trials and three studied post-exposure prophylaxis of household contacts. None of the trials tested efficacy against the current pandemic H1N1 strain.

The main findings reported are as follows:

- Treatment (n=1,766):

Two studies evaluated oseltamivir and two zanamivir; 1,243 had confirmed influenza and the majority had influenza A (55-69%). Three trials recruited otherwise healthy children and a fourth included children with asthma. Treatment with a neuraminidase inhibitor reduced the median time to resolution of symptoms or return to normal activities (or both) by 0.5 - 1.5 days; however this was statistically significant in only two trials. Oseltamivir was not found to reduce asthma exacerbations or improve peak flow in children with asthma (one trial). Treatment was not associated with reduction in overall use of antibiotics (2 trials; risk difference -0.30 [-0.13 to 0.01]). Two trials found no overall effect on the incidence of otitis media in children aged 5-12 years (risk difference -0.01 [-0.04 to 0.02]; P=0.92) although a third found a reduced incidence (from 31% to 15%) in children aged 1 to 5 (0.16 [-0.29 to -0.04], P=0.009).

- Post-exposure prophylaxis (n=863):

Two studies evaluated zanamivir and one oseltamivir. A 10 day course of post-exposure prophylaxis with either drug resulted in an 8% (95% CI 5% to 12%) decrease in the incidence of symptomatic influenza. Zanamivir was well tolerated, but oseltamivir was associated with an increased risk of vomiting (0.05 [0.02 to 0.09], number needed to harm=20).

The authors discuss the strengths and weaknesses of their research, and the implications for seasonal and pandemic influenza. They conclude that neuraminidase inhibitors seem to have a small effect for children with seasonal influenza, and there is currently no evidence to suggest children with asthma should be treated differently.

They comment that “it is difficult to know the extent to which these findings can be generalised to children in the current A/H1N1 pandemic. At present, most cases in children have been mild, but recommendations in several countries encourage treatment of children with suspected or confirmed A/H1N1 flu. While morbidity and mortality in the current pandemic remain low, a more conservative strategy might be considered prudent, given the limited data, side effects such as vomiting, and the potential for developing resistant strains of influenza.”

In terms of prophylaxis, they note that the magnitude of the effect of neuraminidase inhibitors as part of a containment strategy is now clear – 13 people need to be treated to prevent one additional case. “In a prolonged pandemic, however, those most likely to be treated (such as healthcare professionals) might require multiple courses as the number of contacts escalates.”

See the NPCi blog at <http://www.npci.org.uk/blog/?p=552> and patient decision aids for oseltamivir are available at http://www.npci.org.uk/therapeutics/infect/commonintro/patient_decision_aids/patient_decision_aid1.php

1. BMJ 2009; 339:b3172

Neuraminidase inhibitors in adults

A systematic review and meta-analysis concludes that while neuraminidase inhibitors can reduce the duration of seasonal flu in healthy adults by half to one day, overall their use in otherwise healthy adults is unlikely to be appropriate¹.

This review was carried out on behalf of NICE, with the aim of evaluating the effectiveness and cost-effectiveness of prescribing oseltamivir and zanamivir for seasonal influenza in otherwise healthy individuals and those with co-morbidities. It is intended to inform an update of current NICE guidance on the subject (TA58). A previously published reliable systematic review was used to identify relevant controlled trials published before 2001, and a comprehensive literature search used to identify any subsequent published and unpublished studies. Eligible trials compared a neuraminidase inhibitor with placebo, best symptomatic care, or each other. Results were evaluated for healthy adults (i.e. adults without known co-morbidities) and people at-risk of influenza-related complications.

There were 26 relevant trials, 13 each for zanamivir and oseltamivir. For zanamivir, six trials (n=2701) compared the drug with placebo in otherwise healthy adults, and seven trials (n=1,252) in the overall at risk population; four trials (n=1,410) compared oseltamivir with placebo in otherwise healthy people and six (n=1,472) compared it with placebo in patients with co-morbidities.

Overall, zanamivir reduced the median time to symptom alleviation in healthy adults by 0.57 days (95% CI -1.07 to -0.08; p=0.02), and oseltamivir 0.55 days (95% CI -0.96 to -0.14; p=0.008). In those at risk, zanamivir reduced the median time to symptom alleviation by 0.98 days (95% CI -1.84 to -0.11; p=0.03), and oseltamivir reduced it by 0.74 days (95% CI -1.51 to 0.02; p=0.06).

The authors discuss the various options available and conclude that “In view of the advantages and disadvantages of different management strategies for controlling seasonal influenza in healthy adults, recommending the use of antiviral drugs for the treatment of people presenting with symptoms is unlikely to be the most appropriate course of action.” For people who are at increased risk of suffering influenza-related complications, “it is reasonable to recommend precautionary treatment”.

See the NPCi blog at <http://www.npci.org.uk/blog/?p=560> and patient decision aids for oseltamivir are available at http://www.npci.org.uk/therapeutics/infect/commonintro/patient_decision_aids/patient_decision_aid1.php

1. Lancet Infect Dis 2009; 9: 537-45

First-line drugs for hypertension

Ever been troubled by the question “what class of drug to use first-line for lowering blood pressure?”? A recent Cochrane review answers that question¹.

Main results

Of 57 trials identified, 24 trials with 28 arms, including 58,040 patients met the inclusion criteria.

Thiazides (19 RCTs) reduced mortality (RR 0.89, 95% CI 0.83 - 0.96), stroke (RR 0.63, 95% CI 0.57 - 0.71), coronary heart disease {CHD} (RR 0.84, 95% CI 0.75 - 0.95) and cardiovascular events {CVS} (RR 0.70, 95% CI 0.66 - 0.76). Low-dose thiazides (8 RCTs) reduced CHD (RR 0.72, 95% CI 0.61 - 0.84), but high-dose thiazides (11 RCTs) did not (RR 1.01, 95% CI 0.85 - 1.20).

Beta-blockers (5 RCTs) reduced stroke (RR 0.83, 95% CI 0.72 - 0.97) and CVS (RR 0.89, 95% CI 0.81 - 0.98) but not CHD (RR 0.90, 95% CI 0.78 - 1.03) or mortality (RR 0.96, 95% CI 0.86 - 1.07).

ACE inhibitors (3 RCTs) reduced mortality (RR 0.83, 95% CI 0.72 - 0.95), stroke (RR 0.65, 95% CI 0.52 - 0.82), CHD (RR 0.81, 95% CI 0.70 - 0.94) and CVS (RR 0.76, 95% CI 0.67 - 0.85).

Calcium-channel blocker (1 RCT) reduced stroke (RR 0.58, 95% CI 0.41 - 0.84) and CVS (RR 0.71, 95% CI 0.57 - 0.87) but not CHD (RR 0.77 95% CI 0.55 - 1.09) or mortality (RR 0.86 95% CI 0.68 - 1.09).

No RCTs were found for ARBs or alpha-blockers.

Authors' conclusions

First-line low-dose thiazides reduce all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust. First-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides.

Plain language summary

Thiazides best first choice for hypertension

One of the most important decisions in treating people with elevated blood pressure is what drug class is used first. This decision has enormous consequences in terms of health outcomes and cost. In this review health outcomes resulting from 4 drug classes are summarised. Most of the evidence demonstrated that first-line low-dose thiazides reduce mortality and morbidity (stroke, heart attack and heart failure). No other drug class improved health outcomes better than low-dose thiazides, and beta-blockers and high-dose thiazides were inferior. Low-dose thiazides should be the first choice drug in most patients with elevated blood pressure. Fortunately, thiazides are also very inexpensive.

A very sophisticated and complex meta-analysis of 147 RCTs (n=464,000) evaluating the outcomes of blood pressure lowering by drug therapy has also been recently published². Five key questions were posed (including the authors' answers):

1. Do beta-blockers have a special effect in preventing CHD events in people with a clinical history of CHD?
 - Yes. The effect is an approximate 30% reduction in CHD, present for a few years after the infarct. This risk reduction is about 15% thereafter, similar to that of other blood pressure lowering drugs.
2. Does the preventive effect of drugs differ in people with and without a history of cardiovascular disease?
 - No. The percentage reduction in risk of CHD events and stroke is the same or similar. Since the absolute risk is higher in people with a history of cardiovascular disease, however, the absolute risk reduction is greater.
3. Does blood pressure reduction alone explain the preventive effect of the drugs?
 - Yes, except for the special short term effect of beta-blockers.

4. Should the use of blood pressure lowering drugs be limited to people with “high” blood pressure?
 - No. Blood pressure lowering drugs should be offered to anyone with a high enough risk to benefit from treatment whatever their reason for being at high risk, because a given blood pressure reduction lowers risk of CHD and stroke by a constant proportion irrespective of pre-treatment blood pressure.
5. What is the quantitative effect of taking one or more blood pressure lowering drugs on blood pressure and the risk of CHD events and stroke?
 - In people aged 60–69 with a diastolic blood pressure of 90 mmHg (or systolic blood pressure of 150 mmHg): one drug at standard dose lowers the risk of CHD by about 25% and of stroke by 35%; three drugs at half standard dose lower the risk of CHD by 45% and of stroke by 60%; the estimates are about 10 percentage points higher if blood pressure is higher by 30 mmHg systolic or 15 mmHg diastolic; the estimates are about 5 percentage points lower for a 10 year increase in age.

As the NPC points out, there is very little evidence to support the predictions made by the authors for the benefits of using combinations of drugs at half standard dose in comparison with a single drug at standard dose. Supportive evidence from a randomised controlled trial is required before such an approach could be recommended³.

Both of these reviews support the recommendation that low-dose thiazide diuretics are the appropriate first-line choice for most people.

1. *Cochrane Database of Systematic Reviews*, Issue 3, 2009
2. *BMJ* 2009; 338:b1665
3. www.npci.org.uk/blog/?p=353

What BP target?

A randomised open-label trial has tested the hypothesis that tight control of systolic blood pressure compared with usual control in hypertensive patients *without diabetes* would be beneficial¹. The study enrolled 1,111 non-diabetic patients aged 55 years or older with systolic blood pressure greater than 150mmHg (mean 163/90) and one additional risk factor for CV disease, who had been receiving antihypertensive treatment for at least 12 weeks. Patients were randomised to tight (<130mmHg) (n=558) or usual control (<140mmHg) (n=553) and followed up every 4 months for a median of two years. Seven different antihypertensive treatments could be added in on an open-label basis, tailored to the patients’ needs.

At two-year follow-up, systolic blood pressure was less than 130mmHg in 27% of patients in the usual-control group, compared with 72% in the tight-control group (P <0.0001). 17% of patients in the usual-control group had signs of left ventricular hypertrophy (LVH) on electrocardiogram (the primary endpoint), compared with 11% of the tight-control group (odds ratio [OR] 0.63, 95%CI 0.43 to 0.91; P=0.013). A secondary composite CV endpoint occurred in 9% of patients in the usual-control group and 5% of the tight-control group (hazard ratio [HR] 0.50, 95%CI 0.31 to 0.79; P=0.003).

This study showed that it was possible to achieve a target systolic blood pressure below 130mmHg using, on average, three antihypertensive drugs. In addition, reducing blood pressure below this target resulted in a lower likelihood of the primary, disease-oriented outcome, LVH on ECG. LVH is a controversial choice as a sensitive surrogate marker for subsequent cardiovascular events. Although the composite CV secondary endpoint was also statistically significantly reduced, the number of clinical events was very small because of the small sample size and limited follow-up. This means that the study was unlikely to be powered to determine conclusively whether reducing systolic hypertension to 130mmHg reduces CV events.

The accompanying editorial² states that before changing guidelines, a systolic BP treatment goal below 130mmHg should be evaluated in adequately powered randomised trials. Only after that will it be possible to evaluate in which groups of patients such treatment is beneficial, and the cost-effectiveness of such treatment.

The NPC in their blog³ of this study recommends the following action:

“Clinicians should continue to follow the NICE hypertension guideline, which states that the aim of treatment is to reduce blood pressure to 140/90mmHg or below in all people with readings of 160/100mmHg or more, or more

than 140/90mmHg if they have cardiovascular disease, their risk of CV disease is more than 20% over ten years, or they have target organ damage. Treatment thresholds and targets are lower for people with diabetes.”

1. Lancet 2009; 374:525-33
2. Lancet 2009; 374:503-4
3. www.npci.org.uk/blog/?p=506

Update on statins

A meta-analysis of randomised trials that focused on primary prevention has recently been published¹. The primary endpoint was all-cause mortality. Secondary endpoints were the composite of major coronary events (death from CHD and non-fatal MI), and the composite of major cerebrovascular events (fatal and non-fatal stroke).

Ten trials were included in the meta-analysis (n=70,388). 34% of the participants were women and 23% had *diabetes mellitus*. The mean follow-up was 4.1 years. Treatment with statins significantly reduced the risk of all-cause mortality (OR 0.88, 95% CI 0.81 to 0.96), major coronary events (OR 0.70, CI 0.61 to 0.81), and major cerebrovascular events (OR 0.81, CI 0.71 to 0.93). No evidence of an increased risk of cancer was observed.

It is more helpful if the results are presented as NNTs:

Primary prevention; mean age 63 years (55.3 to 75.0); mean follow-up 4.1 years

	NNT
All-cause mortality	167
Major coronary event	77
Major cerebrovascular event	250

The included trials represented participants with a clinically heterogeneous level of risk. Therefore, the benefit observed in the pooled estimate of treatment effect could be of different magnitude depending on the level of risk. Importantly, people with diabetes were included in this meta-analysis and they are normally treated as secondary prevention with respect to statin therapy. The NNTs for primary prevention in those without diabetes are therefore likely to be higher than the pooled estimate.

Compare these NNTs with the NNTs from a meta-analysis of statins for secondary prevention in elderly patients²:

Secondary prevention; mean age range 66.8 to 75.6 years; mean follow-up 4.9 years

	NNT
All-cause mortality	28
Non-fatal MI	38
Stroke	58

The clear message is that the higher the risk, the greater the potential benefit i.e. the lower the NNTs. Secondary prevention with statins is the priority.

A narrative review estimates that the incidence of statin-related myopathy in practice is higher than might be expected from data reported in clinical trials³. Statin-related myalgia may occur in 5-10% of people, and its development appears to be related to dose. However, the incidence of rhabdomyolysis is relatively rare – about 10 to 20 cases per 100,000 person years.

The NPC⁴ recommend the following action:

“Health professionals should be aware that myalgias may occur in up to 10% of patients prescribed statins, although rhabdomyolysis is rare. The development of statin-related myopathy appears to be related to dose, and occurs with **all** statins. **There is no good evidence to suggest that any one statin has any advantages over another in this regard at a population level.** However, the trend for greater use of high-dose statin regimens to chase low LDL cholesterol targets may increase the prevalence of statin-related myopathy. Clinicians should follow NICE guidance on lipid management and use simvastatin 40mg/day for primary and secondary prevention.”

1. BMJ 2009; 338:b2376
2. J Am Coll Cardiol 2008; 51:37-45
3. Ann Intern Med 2009; 150:858-68
4. www.npci.org.uk/blog/?p=370

NICE guideline for low back pain

[NICE CG88](#) covers the early management of persistent non-specific low back pain. This is defined as pain present for more than 6 weeks and less than one year.

Information and education

- Offer educational advice that:
 - Includes information on the benign nature of non-specific low back pain (tension, soreness and/or stiffness in the lower back region arising from several structures in the back, including joints, discs, and connective tissues)
 - Encourages the person to be physically active and continue with normal activities as far as possible.
- Take into account the person's expectation and preferences but do not use their expectations and preferences to predict their response to treatments.

Therapies

Offer one of the following treatment options, taking into account the patient's preference:

- A structured exercise program, either individualised or group
- Manual therapy, including spinal manipulation
- Acupuncture
- Drug therapy: paracetamol first-line, then NSAIDs and/or weak opioids (consider strong opioids for short-term use in severe pain); tricyclic antidepressant if other medication insufficient
- Combined physical and psychological treatment for those who have received at least one less intensive treatment and also have high disability and/or substantial psychological distress

Do not offer

- Radiography of the lumbar spine
- Selective serotonin reuptake inhibitors for treating pain
- Injections of therapeutic substances into the back
- Laser therapy
- Interferential therapy (electrical treatment using two alternating medium frequency currents)
- Therapeutic ultrasonography
- Transcutaneous electrical nerve stimulation (TENS)
- Lumbar supports (devices to reduce spinal mobility, such as corsets)
- Spinal traction

Do not refer for

- Radiofrequency facet joint denervation
- Intradiscal electrothermal therapy
- Percutaneous intradiscal radiofrequency thermocoagulation

JAPC has discussed the drug therapy recommendations and agreed that there should be no change to current local guidance on the use of coxibs and co-prescribing of PPIs with NSAIDs. Coxibs remain BROWN drugs and co-prescribing of PPIs should not be routine but targeted to those at highest risk of a GI bleed.

Ranolazine

MTRAC has published its [review of ranolazine](#). They conclude that ranolazine cannot be recommended for prescribing because the current evidence for its efficacy and safety is inadequate to support its use. Only one RCT has been published that demonstrated efficacy within the licensed indication and dose range, and the effect sizes were considered to be very small. Ranolazine has been associated with QTc prolongation and syncope, and contraindications include some other cardiac agents. Alternative, well established drugs are available for the treatment of chronic stable angina, which gives ranolazine a very low place in therapy.

In Derbyshire, ranolazine is classified as a BROWN drug.