と比較して、米国・英国の添付文書では、妊娠期の薬物動態の変化、具体的な投与量、投与方法の変更の目安が具体的に示されている記載となっていることが分かったた。

妊娠した母体では「妊婦－胎盤－胎児」系が確立し、妊娠の進行とともに母体の消化管運動能や分泌能が低下し、血漿容積や総体水分量は増加し、心拍出量や糸球体ろ過量は増加するが、アルブミン濃度は低下し、代謝酵素活性が変化する。こうした母体の生理的な変化は、薬物の体内動態に、潜在的あるいは臨床的インパクトを持って変化を与えている。

妊婦では、血漿プロゲステロン値の上昇により腸管の運動能が低下して、胃内容物排泄速度は 30～50%遅延することが知られている。このため内服した薬物の吸収も遅延する可能性があり、迅速な薬効を期待する状況下では影響が生じる可能性がある。また、妊婦では胃酸の分泌が減少するため胃内pHが上昇することが知られており、溶解と吸収過程を胃の酸度が助長する薬物では、溶解度・吸収量が低下する可能性がある。

また、妊娠の進行に合わせて、胎盤・胎児・羊水量が増大すること、循環血漿量が約 40～50%増加するため母体の総体水分量は増加すると考えられている。こうした体成分の容積増大のため、水溶性の薬物の分布容積が増加する可能性や、最高血中濃度が低下する可能性が考えられる。ただし、臨床的な投与量の変更が必要になるか否かは、他の母体の生理的変化とも関連しており個人差もあることから一様ではない。

妊娠の進行に伴いアルブミン産生量は増加するがこれを上回る循環血漿量の大幅な増加が生じるため希釈性の低アルブミン血症が生じる。さらに、妊娠週数の進行とともにエストロゲンやプロゲステロン等の女性ホルモンや遊離脂肪酸の血中濃度が増大するために、タンパク結合率が低下することが知られている。

こうした母体の生理学的変化は非結合型の薬物の増加を示唆しているが、非結合型の薬物は薬物代謝酵素の標的となること、妊娠中に増大した腎クリアンスによって排泄されることにより、顕著な変化には至らない薬物もあり個別医薬品の情報が添付文書等で提供されることが望まれる。

この他、妊娠中は増大したエストロゲンやプロゲステロンレベルの影響を受けて、薬物の代謝が変化することが報告されている。薬物の第1相の代謝を担うチトクローム P450 群に属する酵素は、その分子種により妊娠中の活性が上がるもの、低下するもの、大きくは変わらないものが知られている。カフェインの代謝に関与する CYP1A2 は妊娠第1三半期に活性が33%低下し妊娠第3三半期には 65%の低下が報告されている。フェニトインの代謝に関与する CYP2C9 は妊娠第3三半期には20%の増加が報告されているが、フェニトインの代謝に関与する CYP2C19 は妊娠第3三半期には50%の低下が報告されている。

こうした代謝酵素活性の変化は、その妊婦が EM(extensive metabolizer)の場合に顕著に表れ、PM (poor metabolizer)の場合では大きな違いに現れないことが知られており反応性が異なることも考慮しなければならないが、処方設計する薬剤師にとっても、処方するいしにとっても用量調節の必要性があるのか否か、並びにどの様な変化が予想されるのかに関して、科学的根拠が添付文書により提供されることは、妊娠期の薬物療法の有効性と安全性を担保する意味でも、胎児への曝露を最小限にとどめる意味でも重要なことと考えられる。

さらに、第 2 相の薬物代謝を担うグルクロン酸抱合能はバルプロ酸などで増加していることが報告されているが、アセトアミノフェンなどの硫酸抱合は減少していたことが報告されている。

近年、特に注目されているのは、ラモトリギンに関してである。ラモトリギン

単剤で治療している場合、妊娠第 1 三半期～第 2 三半期において活性が 200%増加し、妊娠第 3 三半期には 300%の増加が認められることが報告されている。

一方、腎排泄型の薬物の薬物動態に変化を与える大きな要因は GFR であることが知られている。妊娠中は糸球体ろ過量が約 50%増加することが知られており、腎排泄型薬物であるジゴキシン、リチウム、ペニシリン系・セフェム系等の多くのβラクタム系抗生物質などの腎クリアランスが増加し、薬物血中濃度が低下する可能性が考えられている

今後、我が国における添付文書の記載要領改訂にあたっては、妊娠中の用法・用量の調節について直接的な注意喚起が可能な記載要領に改訂するとともに、この根拠となる情報を記載しうる項目が必要と考えられた。

E. 結論

米国では、2008 年の官報告示により医療用医薬品添付文書における妊婦への投薬に関する記載を大幅に改善する案が示されている。ここでは妊婦への投薬により子宮内で曝露された胎児へのリスクに関する記載のみならず、妊娠女性への処方方針決定の根拠情報として、妊娠中の用法・用量の調節についての情報を含める必要性が示されていた。

今回調査した 5 品目の医薬品に関して、米国・英国では、妊娠期の薬物動態学的な変化や、これに基づく用法・用量の調節に関する記載が充実している結果が得られた。今後、添付文書の記載要領改訂にあたっては、妊娠中の用法・用量の調節についての情報を記載しうる項目が必要と考えられた。

F. 研究発表

1．論文発表

現時点で計画されていない。

2．学会発表

日本医薬品情報学会における発表を予定している。

G. 知的財産権の出願・登録状況（予定含）

1．特許取得

現時点で計画されていない。

2．実用新案登録

現時点で計画されていない。

3．その他

## Digoxin Tablets BP 125 micrograms

Table of Contents

1. Name of the medicinal product
DIGOXIN TABLETS BP 125 micrograms

2. Qualitative and quantitative composition
Each tablet contains 125 micrograms Digoxin PhEur.

3. Pharmaceutical form
White uncoated tablets.
White, circular, flat bevelled-edge, uncoated tablets impressed "C" on one face and the identifying letters "DF" on the reverse.

4. Clinical particulars

4.1 Therapeutic indications
- Digoxin is indicated for the treatment of congestive cardiac failure.
- Digoxin may be used for certain supraventricular dysrhythmias, particularly atrial fibrillation.

4.2 Posology and method of administration
The following schedules are intended as an initial guide but each patient has to be tailored individually according to age, lean body weight and renal function for his/her needs:

Adults and children over 10 years:
Rapid oral loading:
750-1500micrograms (0.75mg-1.5mg) as a single dose. If a greater risk or less urgency eg the elderly, the oral loading dose should be given in divided doses 6 hours apart, assessing clinical response, before giving each additional dose.

Slow oral loading:
250-750micrograms (0.25mg-0.75mg) should be given daily for 1 week, followed by appropriate maintenance dose. A clinical response should be seen within one week.

NB
The clinical state of the patient and the urgency of the condition will depend on the choice between slow or rapid oral loading
The maintenance dosage should be based upon the percentage of the peak body stores lost each day through elimination. The following formula has had wide clinical use:

Maintenance dose:
is peak body stores x (% daily loss ÷ 100)

Where: peak body stores = loading dose; % daily loss = 14 + creatinine clearance (Ccr)/5.

Ccr is creatinine clearance corrected to 70kg body weight or 1.73m2 body surface area. If only serum creatinine (Scr) concentrations are available, a Ccr (corrected to 70kg body weight) may be estimated in men as:

NB:
Serum creatinine values are in micromol/l, these can be converted to mg/100ml (mg/%) as follows:

Where: 113.12 is the molecular weight of creatinine.

For Women: Multiply the result by 0.85.
NB

This formulae cannot be used for creatinine clearance in children.

In practice, this will mean that most patients will be maintained on 0.125 to 0.25mg digoxin daily, however, in those who show increased sensitivity to the adverse effects of digoxin, a dosage of 62.5microgram (0.0625mg) daily or less may suffice. Conversely, some patients may require a higher dose.

Children up to 10 years: (No cardiac glycosides have been given in preceding two weeks.)

Oral loading dose: This should be administered in accordance with the following schedule: pre-term neonates less than 1.5kg (25 micrograms/kg body weight over 24 hours); pre-term neonates 1.5-2.5kg (30 micrograms/kg body weight over 24 hours); term neonates to 2 years (45 micrograms/kg body weight over 24 hours); 2-5 years (35 micrograms/kg body weight over 24 hours); 5-10 years (25 micrograms/kg body weight over 24 hours).

The loading dose should be administered in divided doses with approximately half the total dose given as the first dose, and further fractions of the total dose given at intervals of 4-8 hours, assessing clinical response before giving each additional dose.

Maintenance: The maintenance dose should be administered in accordance with the following schedule: pre-term neonates (daily dose is 20% of 24 hour loading dose); term neonates and children up to 10 years (daily dose is 25% of 24 hour loading dose).

These dosage schedules are meant as guidelines and careful clinical observation and monitoring of serum digoxin levels should be used as a basis for adjustment of dosage in these paediatric patient groups. If cardiac glycosides have been given in the two weeks preceding commencement of digoxin therapy, it should be anticipated that optimum loading doses of digoxin will be less than those recommended above.

Monitoring

Measurements of plasma levels of digoxin are useful in individualising therapy during the early stages of treatment, for detecting poor patient compliance and for diagnosing toxicity. Serum concentrations of digoxin may be expressed in conventional units of ng/ml or SI units of nmol/L. To convert ng/ml to nmol/L, multiply ng/ml by 1.28.

The serum concentration of digoxin can be determined by radioimmunoassay. Blood should be taken 6 hours or more after the last dose of digoxin. There are no rigid guidelines as to the range of serum concentrations that are most efficacious but most patients will benefit, with little risk of toxic symptoms and signs developing, with digoxin concentrations from 0.8 nanogram/ml, ng/ml (1.02 nanomol/litre, nm/L) to 2.0ng/ml (2.56nm/L). Above this range toxic symptoms and signs become more frequent and levels above 3ng/ml (3.84nm/L) are quite likely to be toxic. However, in deciding whether a patient's symptoms are due to digoxin, the patent's clinical state together with the serum potassium level and thyroid function are important factors. Other glycosides, including metabolites of digoxin, can interfere with the assays that are available and one should always be wary of values, which do not seem commensurate with the clinical state of the patient.

Elderly

The tendency to impaired renal function and low lean body mass in the elderly influences the pharmacokinetics of digoxin, such that high serum digoxin levels and associated toxicity can occur quite readily, unless dosages of digoxin lower than those in non-elderly patients are used. Serum digoxin levels should be checked regularly and

hypokalaemia avoided.

Renal impairment

Loading and maintenance doses of digoxin should be reduced as outlined above in patients with impaired renal function because the major route of elimination is renal excretion of unchanged drug.

Thyroid disease

Administering digoxin to a patient with thyroid disease requires care. Initial and maintenance doses of digoxin should be reduced when thyroid function is subnormal. In hyperthyroidism there is relative digoxin resistance and the dose may have to be increased. During the course of treatment of thyrotoxicosis, dosage should be reduced as the thyrotoxicosis comes under control.

Gastrointestinal disease

Patients with malabsorption syndrome or gastrointestinal reconstruction may require larger doses of digoxin.

Method of Administration

For oral administration.

4.3 Contraindications

• Patients known to be hypersensitive to digoxin, other digitalis glycosides or any of the excipients.

· Patients with arrhythmias caused by cardiac glycoside intoxication.

· Patients with hypertrophic obstructive cardiomyopathy, unless there is concomitant atrial fibrillation and heart failure, but even then caution should be exercised if digoxin is to be used.

· Patients with supraventricular arrhythmias associated with an accessory atrioventricular pathway, as in the Wolff-Parkinson-White syndrome, unless the electrophysiological characteristics of the accessory pathway and any possible deleterious effect of digoxin on these characteristics have been evaluated. If an accessory pathway is known or suspected to be present and there is no history of previous supraventricular arrhythmias, digoxin is similarly contraindicated.

· Patients with intermittent complete heart block or second degree atrioventricular block, especially if there is a history of Stokes-Adams attacks.

· Patients with ventricular tachycardia or ventricular fibrillation.

4.4 Special warnings and precautions for use

• Arrhythmias

Arrhythmias may be precipitated by digoxin toxicity, some of which can resemble arrhythmias for which the drug could be advised (e.g. atrial tachycardia with varying

atrioventricular block requires care as clinically the rhythm resembles atrial fibrillation).

In some cases of sinoatrial disorder (i.e. sick sinus syndrome) digoxin may cause or exacerbate sinus bradycardia or cause sinoatrial block.

· Hypokalaemia, hypomagnesaemia, hypercalcaemia

Hypokalaemia sensitises the myocardium to the actions of cardiac glycosides. Digoxin should be used with caution in patients taking drugs that may cause hypokalaemia (see section 4.5). Hypokalaemia may also accompany malnutrition, diarrhoea, vomiting and long standing wasting disease and the dose may be need to be reduced in such patients. Hypomagnesaemia and marked hypercalcaemia also increase myocardial sensitivity to cardiac glycosides.

· Direct current cardioversion

Direct current cardioversion is the preferred method of treatment for atrial flutter. The risk of provoking dangerous arrhythmias with direct current cardioversion is greatly increased in the presence of digitalis toxicity and is in proportion to the cardioversion energy used.

For elective direct current cardioversion of a patient who is taking digoxin, the drug should be withheld for 24 hours before cardioversion is performed. In emergencies, such as cardiac arrest, when attempting cardioversion the lowest effective energy should be applied. Direct current cardioversion is inappropriate in the treatment of arrhythmias thought to be caused by cardiac glycosides.

· Myocardial infarction

The administration of digoxin in the period immediately following myocardial infarction is not contraindicated. However, the possibility of arrhythmias arising in patients who may be hypokalaemic after myocardial infarction and are likely to be cardiologically unstable must be borne in mind. The limitations imposed thereafter on direct current-cardioversion must also be remembered.

· Chronic congestive heart failure

Although many patients with chronic congestive cardiac failure benefit from acute administration of digoxin, there are some in which it does not lead to constant, marked or lasting haemodynamic improvement. It is therefore important to evaluate the response of each patient individually when digoxin is continued long-term.

· Severe respiratory disease

Patients with severe respiratory disease may have increased myocardial sensitivity to digitalis glycosides.

· Gastrointestinal disease

Patients with malabsorption syndrome or gastrointestinal reconstruction may require larger doses of digoxin.

· Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take digoxin.

4.5 Interaction with other medicinal products and other forms of interaction

These may arise from effects on the renal excretion, tissue binding, plasma protein binding, distribution within the body, gut absorptive capacity and sensitivity to digoxin. Consideration of the possibility of an interaction whenever concomitant therapy is contemplated is the best precaution and a check on serum digoxin level is recommended when any doubt exists.

· Antiarrhythmics

Amiodarone: plasma levels of digoxin are considerably increased by concurrent administration of amiodarone. This is due to a decrease in the renal and non-renal clearance of digoxin, a prolongation of its half life and a possible increase in absorption. Children are especially sensitive. The dose of digoxin should be reduced by a third to a half when it is given concurrently with amiodarone. Disopyramide may modify the cardiovascular effects of digoxin and reduce its volume of distribution. The loading dose of digoxin should be reduced in patients who are also receiving disopyramide. Flecainide: plasma levels of digoxin are increased by concurrent administration of flecainide. This is likely to be clinically significant only in patients with high plasma levels of digoxin or those with atrioventricular nodal dysfunction. Moracizine: digoxin and moracizine have additive effects on cardiac conduction. Propafenone: plasma levels of digoxin are increased by concurrent administration of propafenone. There is considerable interindividual variation in the extent of this interaction but the dose of digoxin should be reduced and patients monitored for signs of digoxin toxicity. Quinidine: the renal and non-renal excretion of digoxin is reduced by co-administration of digoxin. Excretion in bile and tissue binding of digoxin may also be reduced Significant effects occur as soon as quinidine is given to a patient stabilised on digoxin and plasma levels of digoxin are usually doubled within 5 days. The dose of digoxin should be halved when quinidine is added to therapy and the possibility of an alternative anti-arrhythmic should be examined.

· Anti-infective drugs

Macrolides, tetracycline: presystemic metabolism of digoxin to inactive metabolites in the gastrointestinal tract occurs in about 10% of patients. Co-administration of macrolide antibiotics (azithromycin, clarithromycin, erythromycin, telithromycin) or tetracycline to this sub-group of patients can result in a clinically significant increase in plasma digoxin levels. Neomycin: absorption of digoxin from the gastrointestinal tract is inhibited by neomycin and plasma levels are reduced. Rifampicin: the metabolism of digoxin may be increased by co-administration with rifampicin. The interaction may be enhanced in patients with renal impairment. Trimethoprim: the renal excretion of digoxin is decreased by concurrent administration with trimethoprim. The interaction is more significant in elderly patients or those with renal impairment and digoxin plasma levels should be monitored. Amphotericin: hypokalaemia due to amphotericin administration may potentiate digoxin toxicity. Patients should be monitored and given potassium supplements when necessary. Itraconazole can cause a marked increase in plasma digoxin levels and toxicity may occur if the dose of digoxin is not reduced. Itraconazole may also oppose the positive inotropic effects of digoxin. Quinine, hydroxychloroquine and chloroquine can increase plasma levels of digoxin by decreasing non-renal clearance.

· Calcium channel blockers

Diltiazem and digoxin co-administration can result in increased digoxin plasma levels and toxicity and patients should be monitored. Nifedipine may increase digoxin plasma levels but there is considerable interindividual variation. Patients taking high doses of digoxin or those with renal impairment are most at risk. Nisoldipine may also increase plasma levels of digoxin but amlodipine, felodipine, isradipine, lercanidipine, nicardipine, nimodipine and nitrendipine do not appear to have significant effects on digoxin plasma levels but it is prudent to monitor the effects of co-administration. Verapamil increases plasma digoxin levels by inhibiting the active tubular secretion

and non-renal clearance of digoxin. The dose of digoxin should be reduced and plasma levels monitored. Verapamil may also increase atrioventricular block and tachycardia in patients taking digoxin.

· Calcium salts and vitamin D analogues

Intravenous administration of calcium salts to patients taking digoxin can result in dangerous cardiac arrhythmias and should be avoided. Vitamin D analogues can also increase digoxin toxicity due to elevations in plasma calcium concentrations.

· Cardiovascular drugs

ACE inhibitors and angiotensin II antagonists may cause hyperkalaemia which can reduce tissue binding of digoxin resulting in higher serum levels. These drugs may also cause a deterioration in renal function resulting in elevated serum levels of digoxin because of impaired renal excretion. Concurrent administration of captopril has been associated with increases in plasma digoxin levels but this may only be clinically significant in patients with impaired renal function or severe congestive heart failure. Telmisartan administration has been associated with increases in plasma digoxin levels and patients receiving both drugs should be monitored. No clinically significant interactions have been noted with other ACE inhibitors or angiotensin II antagonists examined (cilazapril, enalapril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril and trandolapril; candesartan, eprosartan, irbesartan, losartan and valsartan)) but it is prudent to monitor the effects of co-administration. There is an increased risk of atrioventricular block and bradycardia when digoxin and beta blockers are taken concomitantly. Nitroprusside and hydralazine increase the renal clearance of digoxin by increasing renal blood flow and tubular secretion and lowering plasma digoxin levels.

· Central nervous system drugs

St John's wort: co-administration of digoxin with St John's wort should be avoided because plasma levels are significantly reduced. Nefazodone, trazodone: Plasma levels of digoxin are increased by concomitant administration of nefazodone or trazodone and it may be necessary to reduce the dose of digoxin. Phenytoin increases total clearance of digoxin and reduces its elimination half-life, resulting in a decrease in plasma levels. Intravenous phenytoin should not be used to treat digitalis induced arrhythmias or in patients with a high degree of heart block or marked bradycardia because of the risk of cardiac arrest. Topiramate: co-administration of digoxin and topiramate reduces the bioavailability of digoxin and patients should be monitored. Alprazolam and diazepam can decrease digoxin clearance, resulting in increased plasma concentrations. Patients should be monitored for digoxin toxicity, especially those aged over 65. Digoxin may have detrimental effects on the short term control of bipolar disorder in patients treated with lithium.

· Diuretics

Potassium depletion due to acetazolamide, loop diuretics and thiazide diuretics potentiates the effects of digoxin on the myocardium and may also have a small effect on reducing the renal tubular secretion of digoxin. Patients should be monitored for hypokalaemia and given potassium supplements when necessary. Spironolactone decreases renal excretion of digoxin, increasing plasma levels. The dose of digoxin should be decreased in susceptible patients.

· Gastrointestinal drugs

Antacids and adsorbents, such as kaolin, can inhibit the absorption of digoxin from the gastrointestinal tract, resulting in a fall in digoxin plasma levels. The interaction can be prevented by separating the doses by about 2 hours. Carbenoxolone may cause fluid

retention and hypokalaemia which can increase susceptibility to digoxin toxicity. Metabolism of digoxin in the gastrointestinal tract is inhibited by omeprazole, resulting in increased plasma levels of digoxin. Smaller effects have been seen with pantoprazole and rabeprazole. Sucralfate decreases the absorption of digoxin from the gastrointestinal tract, lowering plasma levels. Plasma levels of digoxin may be reduced by co-administration with sulfasalazine because of decreased absorption. Patients receiving both drugs should be monitored. No interaction has been seen between digoxin and another mesalazine prodrug, balsalazide.

· Lipid regulating drugs

Increases in plasma levels of digoxin have been observed in patients taking atorvastatin and it may be necessary to reduce the dose of digoxin. Although fluvastatin, pravastatin and simvastatin do not appear to cause significant increases in plasma digoxin levels it is prudent to monitor the effects of co-administration. Colestipol and colestyramine bind to digoxin in the gastrointestinal tract, reducing its absorption and lowering plasma digoxin levels. The interaction can be prevented by separating the doses of digoxin and anion exchange resin by about 2 hours.

· Muscle relaxants

Edrophonium should not be given to patients with atrial flutter and tachycardia who are taking digoxin as the combination may cause excessive bradycardia and atrioventricular block. Serious cardiac arrhythmias can develop in patients taking digoxin if they are given suxamethonium and pancuronium due to rapid removal of potassium from myocardial cells. Concomitant use should be avoided. Tizanidine may potentiate hypotension and bradycardia when administered concurrently with digoxin.

· NSAIDs

NSAIDs have the potential to cause renal impairment, reducing the renal clearance of digoxin with a subsequent increase in plasma levels. Aspirin, azapropazone, diclofenac, fenbufen, ibuprofen, indometacin and tiaprofenic acid have all been shown to increase plasma concentrations of digoxin but this may only be clinically significant in patients with impaired renal function. Etoricoxib, ketoprofen, meloxicam, piroxicam and rofecoxib do not appear to increase plasma digoxin levels. Patients being treated with digoxin often need to take NSAIDs and digoxin plasma concentrations should be monitored whenever an NSAID is initiated or discontinued. Phenylbutazone stimulates hepatic metabolism of digoxin so plasma levels should be monitored in these drugs are given concurrently.

· Other drugs

Acarbose inhibits the absorption of digoxin in the gastrointestinal tract, resulting in lower plasma levels. Plasma levels of digoxin are increased by concomitant administration of prazosin. Carbimazole or penicillamine may reduce plasma levels of digoxin. Changes in thyroid function may affect sensitivity to digoxin independently of plasma levels. Increased plasma digoxin levels have been reported when ciclosporin has been administered to patients taking digoxin due to reduced renal elimination. Patients should be monitored closely and the digoxin dose adjusted when required. Corticosteroids cause potassium loss and sodium and water retention which increase the risk of digoxin toxicity and heart failure. Patients taking prolonged courses of corticosteroids should be monitored closely. Many cytotoxic drugs damage the intestinal lining, impairing the absorption of digoxin and decreasing plasma levels. The effect is reversed shortly after discontinuing cytotoxic drug administration. Selective beta2 agonists may cause hypokalaemia which can increase susceptibility to digoxin induced arrhythmias. Concurrent administration of salbutamol has also been associated with increases in plasma digoxin levels.

4.6 Pregnancy and lactation

• Pregnancy

No data are available on whether or not digoxin has teratogenic effects.

There is no information available on the effect of digoxin on human fertility.

The use of digoxin in pregnancy is not contraindicated, although the dosage and control may be less predictable in pregnant than in non-pregnant women with some requiring an increased dosage of digoxin during pregnancy. As with all drugs, use should be considered only when the expected clinical benefit of treatment to the mother outweighs any possible risk to the developing foetus.

Despite extensive antenatal exposure to digitalis preparations, no significant adverse effects have been observed in the foetus or neonate when maternal serum digoxin concentrations are maintained within the normal range. Although it has been speculated that a direct effect of digoxin on the myometrium may result in relative prematurity and low birthweight, a contributing role of the underlying cardiac disease cannot be excluded. Maternally administered digoxin has been used successfully to treat foetal bradycardia and congestive heart failure.

· Breast feeding

Although digoxin is excreted in breast milk, the quantities are minute and breast feeding is not contraindicated.

4.7 Effects on ability to drive and use machines

Neurological adverse effects and visual disturbances have been reported in patients receiving digoxin. Patients should make sure they are not affected before they drive or operate machinery.

4.8 Undesirable effects

The adverse effects produced by digoxin are frequently due to the narrow margin between therapeutic and toxic doses. Plasma levels in excess of 2nmol.L-1 indicate that the patient is at special risk, although there is considerable interindividual variation. Special care should be taken in patients at high risk of developing digoxin toxicity, such as the elderly and those with renal impairment or thyroid disease (see Special warnings, above). In addition, care should be taken when digoxin is taken with other medications as many have the potential to affect plasma digoxin concentrations or electrolytes and cause toxicity (see section 4.5).

· Blood and lymphatic system disorders

Thrombocytopenia has been reported in patients taking digoxin. Agranulocytosis has been reported rarely.

· Immune system disorders

Hypersensitivity reactions have been reported rarely in patients taking digoxin. These include pruritus, erythematous rashes, papules, vesicles and angioedema.

· Endocrine disorders

Digoxin has oestrogenic activity and is associated with gynaecomastia in men following prolonged administration.

· Psychiatric disorders

Digoxin is associated with disorientation, mental confusion, amnesia and depression. Acute psychosis, delirium, visual and auditory hallucinations have been reported rarely, especially in elderly patients. Epilepsy has been reported rarely.

· Nervous system disorders

Neurological effects are also common symptoms of excessive digoxin dosage. They include headache, fatigue, weakness, dizziness, drowsiness, bad dreams, restlessness, nervousness, agitation and apathy.

· Eye disorders

Visual disturbances, including blurred vision and photophobia, may occur. Colour vision may be affected infrequently, with objects appearing yellow or, less frequently, green, red, blue, brown or white.

· Cardiac disorders

The most serious adverse effects of digoxin are on the heart. Usually an early stage of digoxin toxicity is the occurrence of ventricular premature contractions; they can proceed to bigeminy or even trigeminy. Toxic doses may cause or aggravate heart failure. Supraventricular or ventricular arrhythmias and defects of conduction are common and may be an early indication of excessive dosage. The underlying heart condition influences the occurrence and severity of arrhythmias. Supraventricular tachycardia, especially atrioventricular node junctional tachycardia and atrial tachycardia with block are particularly indicative of digoxin toxicity. Ventricular arrhythmias, including extrasystoles, sinoatrial block, sinus bradycardia and atrioventricular block, may also occur.

· Gastrointestinal disorders

Centrally mediated anorexia, nausea and vomiting may be early signs of an excessive dose of digoxin. Abdominal pain and diarrhoea may occur, particularly in elderly patients. Intestinal ischaemia which responds to verapamil has been reported rarely.

Undesirable effects in children

Children are especially sensitive to the effects of digoxin (see section 4.2). Anorexia, nausea, vomiting, diarrhoea and CNS disturbances may occur but they are rarely the initial symptoms of overdose. Cardiac arrhythmias are the most frequent sign of excessive dosing with digoxin. The most common are conduction disturbances or superventricular tachyarrhythmias, such as atrial tachycardia with or without block. Ventricular arrhythmias are less common. Sinus bradycardia may indicate digoxin toxicity, especially in infants.

4.9 Overdose

After recent ingestion, such as accidental or deliberate self-poisoning, the load available for absorption may be reduced by gastric-lavage. Patients with massive digitalis ingestion should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gastrointestinal tract during enterohepatic recirculation.

An overdosage of digoxin of 10 to 15 mg in adults without heart disease and of 6 to 10mg in children aged 1 to 3 years without heart disease appeared to be the dose resulting in death in half of the patients. If more than 25mg of digoxin was ingested by an adult without heart disease, death or progressive toxicity responsive only to digoxin-binding Fab antibody fragments resulted. If more than 10mg of digoxin was ingested by a child aged 1 to 3 years without heart disease, the outcome was uniformly fatal when Fab fragment treatment was not given.

If hypokalaemia is present, it should be corrected with potassium supplements either orally or intravenously depending on the urgency of the situation. In cases where a large amount of digoxin has been ingested, hyperkalaemia may be present due to release of potassium from skeletal muscle. Before administering potassium in digoxin overdose the serum potassium level must be known.

Bradyarrhythmias may respond to atropine but temporary cardiac pacing may be required. Ventricular arrhythmias may respond to lidocaine or phenytoin.

Dialysis is not particularly effective in removing digoxin from the body in potentially life-threatening toxicity.

Rapid reversal of the complications that are associated with serious poisoning by digoxin, digitoxin and related glycosides has followed intravenous administration of digoxin specific (ovine) antibody fragments (Fab) (Digibind®) when other therapies have failed.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

ATC code: C01AA05 Cardiac glycosides

The pharmacological receptor of digoxin is the membrane bound cation dependent sodium- and potassium-linked adenosine triphosphatase (Na+,K+ATPase). Digoxin binds to this enzyme and inhibits it, resulting in an increase in the intracellular concentration of calcium which, in turn, alters the intracellular disposition of calcium.

The effect of digitalis on intracellular calcium concentrations results in an increase in the force and velocity of myocardial systolic contraction (i.e. a positive inotropic effect on myocardial cells). Digoxin has a negative chronotropic effect as it slows the overall heart rate. These actions result in a decrease in the rate of contractility, particularly through the atrioventricular node, with subsequent effects on atrial fibrillation. Digoxin also has complex direct effects on conduction velocities and refractory periods of the conducting fibres in cardiac muscle. In addition to its direct effects, digoxin acts indirectly by increasing vagal input through direct vagal stimulation and decreasing sympathetic drive. These effects contribute to the slowing of the ventricular rate by digoxin, both in sinus rhythm and in atrial fibrillation.

### 5.2 Pharmacokinetic properties

- Absorption

Digoxin is incompletely (about 70%) absorbed from the gastrointestinal tract, most absorption taking place in the stomach and the upper intestine. Food decreases the rate but not the extent of absorption. The onset of effect occurs within about 2 hours and reaches its maximum after about 6 hours following an oral dose. The generally accepted therapeutic plasma level is 0.8 to 2 nmol.L-1 but there are wide interindividual

variations.

· Distribution

Digoxin has a large volume of distribution and is widely distributed in tissues, including the heart, brain, erythrocytes and skeletal muscles, and it crosses the blood brain barrier. The concentration of digoxin in the myocardium is considerably higher than in plasma. From 20 to 30% of a dose is bound to plasma proteins. The volume of distribution is decreased in patients with renal impairment and hypothyroidism and it is increased in patients with hyperthyroidism.

· Metabolism and elimination

Most of a dose of digoxin is excreted unchanged by the kidneys, although some of the dose is metabolised to pharmacologically active and inactive metabolites. It is subject to glomerular filtration and to active secretion and passive resorption by the renal tubules. The balance between these two mechanisms results in a close relationship between renal clearance of digoxin and creatinine. Bacterial flora in the gastrointestinal tract metabolise digoxin to cardio-inactive metabolites in about 10% of patients. The elimination half-life of digoxin is about 40 hours in patients with normal renal function but it can be prolonged to 96 hours in severe renal impairment.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients
Also contains: lactose, magnesium stearate, maize starch, pregelatinised maize starch.

6.2 Incompatibilities
None known.

6.3 Shelf life
Shelf-life

Three years from the date of manufacture.

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

Not applicable.

6.4 Special precautions for storage
Store below 25°C in a dry place.

6.5 Nature and contents of container
The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene tablet containers with polyfoam wad and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass bottles with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:

a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/$M^2$ PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack sizes: 28s, 30s, 56s, 60s, 84s, 90s, 100s, 112s, 120s, 168s, 180s, 250's, 500's, 1000's

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for temporary storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 50,000.

6.6 Special precautions for disposal and other handling
Not applicable.

Administrative data

7. Marketing authorisation holder
Name or style and permanent address of registered place of business of the holder of the Marketing Authorisation:

Actavis UK Limited

(Trading style: Actavis)

Whiddon Valley

BARNSTAPLE

N Devon EX32 8NS

8. Marketing authorisation number(s)
PL 0142/0127

9. Date of first authorisation/renewal of the authorisation
11.7.79

Renewed: 11.7.84; 16.4.93

10. Date of revision of the text
19/12/2012

Epivir 150 mg film-coated tablets
Table of Contents


## 1. Name of the medicinal product

Epivir® 150 mg film-coated tablets

## 2. Qualitative and quantitative composition

Each film-coated tablet contains 150 mg lamivudine.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Film-coated tablet

White, diamond shaped scored tablets engraved with "GX CJ7" on both faces.

## 4. Clinical particulars

### 4.1 Therapeutic indications

Epivir is indicated as part of antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children.

### 4.2 Posology and method of administration

The therapy should be initiated by a physician experienced in the management of HIV infection.

Epivir may be administered with or without food.

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing. For patients who are unable to swallow tablets, lamivudine is available as an oral solution. Alternatively, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see section 5.2).

Adults and adolescents (over 12 years of age): the recommended dose of Epivir is 300 mg daily. This may be administered as either 150 mg twice daily or 300 mg once daily (see section 4.4). The 300 mg tablet is only suitable for the once a day regimen.

Patients changing to the once daily regimen should take 150 mg twice a day and switch to 300 mg once a day the following morning. Where an evening once daily regimen is preferred, 150 mg of Epivir should be taken on the first morning only, followed by 300

mg in the evening. When changing back to a twice daily regimen patients should complete the days treatment and start 150 mg twice a day the following morning.

Children (under 12 years of age):

Since an accurate dosing cannot be achieved with this formulation, dosing according to weight bands is recommended for Epivir tablets. This dosing regimen for paediatric patients weighing 14-30 kg is based primarily on pharmacokinetic modelling, with supporting data from clinical studies.

For children weighing at least 30 kg: the adult dosage of 150 mg twice daily should be taken.

For children weighing between 21 kg to 30 kg: the recommended oral dose of Epivir (150 mg) is one-half tablet taken in the morning and one whole tablet taken in the evening.

For children weighing 14 to 21 kg: the recommended oral dose of Epivir (150 mg) is one half of a scored tablet taken twice daily.

Epivir is also available as an oral solution for children over three months of age and who weigh less than 14 kg or for patients who are unable to swallow tablets.

Less than three months of age: the limited data available are insufficient to propose specific dosage recommendations (see section 5.2).

Renal impairment: Lamivudine concentrations are increased in patients with moderate - severe renal impairment due to decreased clearance. The dose should therefore be adjusted, using oral solution presentation of Epivir for patients whose creatinine clearance falls below 30 ml/min (see tables).

Dosing recommendations – Adults and adolescents weighing at least 30 kg:

| **Creatinine clearance (ml/min)** | **First dose** | **Maintenance dose** |
|---|---|---|
| ≥50 | 150 mg | 150 mg twice daily |
| 30-<50 | 150 mg | 150 mg once daily |
| <30 | As doses below 150 mg are needed the use of the oral solution is recommended | |

There are no data available on the use of lamivudine in children with renal impairment. Based on the assumption that creatinine clearance and lamivudine clearance are correlated similarly in children as in adults it is recommended that the dosage in children with renal impairment be reduced according to their creatinine clearance by the same proportion as in adults.

Dosing recommendations – Children aged at least 3 months and weighing less than 30 kg:

| **Creatinine clearance (ml/min)** | **First dose** | **Maintenance dose** |
|---|---|---|
| ≥50 | 4 mg/kg | 4 mg/kg twice daily |
| 30 to<50 | 4 mg/kg | 4 mg/kg once daily |
| 15 to <30 | 4 mg/kg | 2.6 mg/kg once daily |
| 5 to <15 | 4 mg/kg | 1.3 mg/kg once daily |

| | | |
|---|---|---|
| <5 | 1.3 mg/kg | 0.7 mg/kg once daily |

Hepatic impairment: Data obtained in patients with moderate to severe hepatic impairment shows that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Based on these data, no dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Epivir is not recommended for use as monotherapy.

Renal impairment: In patients with moderate to severe renal impairment, the terminal plasma half-life of lamivudine is increased due to decreased clearance, therefore the dose should be adjusted (see section 4.2).

Triple nucleoside therapy: There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when lamivudine was combined with tenofovir disoproxil fumarate and abacavir as well as with tenofovir disoproxil fumarate and didanosine as a once daily regimen.

Opportunistic infections: Patients receiving Epivir or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

Transmission of HIV: Patients should be advised that current antiretroviral therapy, including Epivir, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions should continue to be taken.

Pancreatitis: Cases of pancreatitis have occurred rarely. However it is not clear whether these cases were due to the antiretroviral treatment or to the underlying HIV disease. Treatment with Epivir should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

*Lactic acidosis:* lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).
Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.
Lactic acidosis generally occurred after a few or several months of treatment.
Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.
Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.
Patients at increased risk should be followed closely.
Mitochondrial dysfunction: Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown.

Any child exposed in utero to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and Pneumocystis carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Liver disease: If lamivudine is being used concomitantly for the treatment of HIV and HBV, additional information relating to the use of lamivudine in the treatment of hepatitis B infection is available in the Zeffix SPC.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

If Epivir is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis (see Zeffix SPC).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered (see section 4.8).

Osteonecrosis: Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Epivir should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine.

The combination of lamivudine with cladribine is not-recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction
Interaction studies have only been performed in adults

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40 % increase in lamivudine exposure, because of the trimethoprim component; the sulfamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see section 4.2). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration is warranted, patients should be monitored clinically. Co-administration of lamivudine with high doses of co-trimoxazole for the treatment of Pneumocystis carinii pneumonia (PCP) and toxoplasmosis should be avoided.

The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine. The nucleoside analogues (e.g. didanosine) like zidovudine, are not eliminated by this mechanism and are unlikely to interact with lamivudine.

A modest increase in Cmax (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) is not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine (see section 5.2).

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended (see section 4.4).

Lamivudine metabolism does not involve CYP3A, making interactions with medicinal products metabolised by this system (e.g. PIs) unlikely.

4.6 Fertility, pregnancy and lactation
A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative toxicity. Epivir can be used during pregnancy if clinically needed.

For patients co-infected with hepatitis who are being treated with lamivudine and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in infants exposed in utero and/or post-natally to nucleoside analogues (see section 4.4).

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum. Since lamivudine and the virus pass into breast

milk, it is recommended that mothers taking Epivir do not breast-feed their infants. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects
The following adverse reactions have been reported during therapy for HIV disease with Epivir.

The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic systems disorders

Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopenia

Very rare: Pure red cell aplasia

Nervous system disorders

Common: Headache, insomnia

Very rare: peripheral neuropathy (or paraesthesia)

Respiratory, thoracic and mediastinal disorders

Common: Cough, nasal symptoms

Gastrointestinal disorders

Common: Nausea, vomiting, abdominal pain or cramps, diarrhoea

Rare: Pancreatitis. elevations in serum amylase.

Hepatobiliary disorders

Uncommon: Transient elevations in liver enzymes (AST, ALT).

Rare: Hepatitis

Skin and subcutaneous tissue disorders

Common: Rash, alopecia

Rare: Angioedema

Musculoskeletal and connective tissue disorders

Common: Arthralgia, muscle disorders

Rare: Rhabdomyolysis