CONFIDENTIAL

CLEAN PROPOSED PACKAGE INSERT

3TC®

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

3TC® TABLETS

3TC® ORAL SOLUTION

COMPOSITION:

3TC TABLETS:	Each film-coated tablet contains 150 mg lamivudine. *Excipients:* Tablet core: magnesium stearate, microcrystalline cellulose and sodium starch glycollate. Film-coating: hydroxypropylmethyl cellulose, macrogol, polysorbate 80 and titanium dioxide.
3TC ORAL SOLUTION:	Each 1 ml contains 10 mg lamivudine. Contains sugar (sucrose 20 % *m/v*). *Excipients:* artificial banana flavour, artificial strawberry flavour, citric acid anhydrous, methyl hydroxybenzoate (0,15 % *m/v*), propyl hydroxybenzoate (0,018 % *m/v*), propylene glycol, purified water, sodium citrate, sucrose.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Lamivudine is a selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. It is also active against zidovudine-resistant clinical isolates of HIV.

Lamivudine is metabolised intracellularly to the 5'-triphosphate which has an intracellular half-life of 16-19 hours. Lamivudine 5'-triphosphate is a weak inhibitor of the RNA and DNA dependent activities of HIV reverse transcriptase, its mode of action is a chain terminator of HIV reverse transcription.

Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells *in vitro*.

Lamivudine-resistant variants of HIV-1 have been selected *in vitro*. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine residue to either isoleucine or valine. HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients.

Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harbouring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine.

Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Lamivudine-resistant HIV-1 mutants were cross resistant to didanosine and zalcitabine. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received lamivudine therapy. Evidence from clinical studies show that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior antiretroviral therapy.

The relationship between *in vitro* susceptibility of HIV to lamivudine and the clinical response to therapy remain under investigation.

Pharmacokinetic properties:

Pharmacokinetics in adults: Lamivudine is well absorbed from the gastrointestinal tract and the bioavailability of oral lamivudine in adults is normally between 80 % and 85 %. Following oral administration, the mean time (T_{max}) to maximum serum concentration (C_{max}) is about an hour. At therapeutic dose levels i.e. 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1-1,5 µg/ml.

From intravenous studies, the mean volume of distribution is 1,3 ℓ/kg and the mean terminal half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 ℓ/kg/h, with predominantly renal clearance (> 70 %) via active tubular secretion, but little (< 10 %) hepatic metabolism.

No dose adjustment is needed when co-administered with food as lamivudine bioavailability is not altered, although a delay in T_{max} and reduction in C_{max} have been observed.

Administration of tablets is bioequivalent to oral solution with respect to AUC_{∞} and C_{max} in adults.

Absorption differences have been observed between adult and paediatric populations (see Pharmacokinetics in children).

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin.

Lamivudine elimination will be affected by renal impairment, whether it is disease- or age-related. A recommended dosage regimen for patients with creatinine clearance below 50 ml/min is shown in the dosage section.

Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary. The likelihood of adverse drug interactions with lamivudine is low due to the limited metabolism and plasma protein binding and almost complete renal clearance.

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with the 3TC/zidovudine combination in patients with renal impairment should be carefully assessed.

Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2-4 hours after oral administration was approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

***Pharmacokinetics in children*:**

The absolute bioavailability of lamivudine (approximately 58-66 %) was lower and more variable in paediatric patients below 12 years of age. In children, administration of

tablets delivered higher plasma lamivudine AUC_{∞} and C_{max} than oral solution. Children receiving lamivudine oral solution according to the recommended dosage regimen achieve plasma lamivudine exposure within the range of values observed in adults. Children receiving lamivudine oral tablets according to the recommended dosage regimen achieve higher plasma lamivudine exposure than children receiving oral solution because higher mg/kg doses were administered with the tablet formulation and the tablet formulation has higher bioavailability (see DOSAGE AND DIRECTIONS FOR USE). Paediatric pharmacokinetic studies with both oral solution and tablet formulations have demonstrated that once daily dosing provides equivalent AUC_{0-24} to twice daily dosing of the same total daily dose.

There are limited pharmacokinetic data for patients < 3 months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely due to immature renal function and variable absorption.

***Pharmacokinetics in pregnancy*:**

Following oral administration, lamivudine pharmacokinetics in late-pregnancy were similar to non-pregnant adults. Administration of lamivudine in animal toxicity studies at very high doses was not associated with any major organ toxicity. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia. Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an *in vitro* cytogenic assay. Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 30-40 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed in *in vivo* tests it is concluded that 3TC should not represent a genotoxic hazard to patients undergoing treatment. There is as yet no information on the tumorigenic risk in animals, and therefore any potential risk to man must be balanced against the expected benefits of treatment.

INDICATIONS:

3TC in combination with zidovudine is indicated in the treatment of:

- HIV infected adults with progressive immunodeficiency (CD4 count < 500 cells/mm^3) who have no prior antiretroviral therapy.
- HIV infected adults with progressive immunodeficiency who have been previously treated with zidovudine.

3TC is indicated as part of antiretroviral combination therapy for the treatment of HIV infected children.

CONTRA-INDICATIONS:

The use of 3TC is contra-indicated in patients with a known hypersensitivity to lamivudine or to any ingredients of 3TC.

WARNINGS AND SPECIAL PRECAUTIONS:

3TC should not be used as monotherapy.

Lactic acidosis/hyperlactataemia:

Use of 3TC can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/ℓ with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/ℓ with symptoms and/or with reduced standard bicarbonate:

Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism).

- Lactate > 10 mmol/ℓ: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.

Caution should be exercised when administering 3TC to patients with known risk factors for liver disease. Treatment with 3TC should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

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. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether these neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Fat redistribution: Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, elevated serum lipid and glucose levels have been observed either

separately or together in some patients receiving combination antiretroviral therapy (see SIDE EFFECTS).

In addition, the lipodystrophy syndrome has a multi-factorial aetiology; with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles.

The long-term consequences of these events are currently unknown.

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Osteonecrosis: Although the aetiology 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.

Renal impairment: In patients with moderate to severe renal impairment, the terminal half-life of 3TC is increased due to decreased clearance. The dose of 3TC should therefore be adjusted (see DOSAGE AND DIRECTIONS FOR USE).

Liver disease: Use of 3TC can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of 3TC has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines.

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. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

Immune Reconstitution Syndrome: In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections 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 ART. Relevant examples are tuberculosis, cytomegalovirus retinitis, cryptococcal meningitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* (*P. carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-immune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be with atypical presentation.

Pancreatitis: Pancreatitis has been observed in patients receiving 3TC. However, it is unclear whether this was due to the medicine treatment or to underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of 3TC until diagnosis of pancreatitis is excluded.

Opportunistic infections: Patients receiving 3TC or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by physicians experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV-transmission to others: Patients should be advised that antiretroviral therapy, including 3TC, has not been shown to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Patients with HIV and hepatitis B or C co-infection: Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue 3TC should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Discontinuation of 3TC therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Special patient population: *Children*: Children who at anytime received lamivudine oral solution concomitantly with other antiretroviral oral solutions in clinical trials experienced lower rates of virological suppression, had lower plasma lamivudine exposure and developed viral resistance more frequently than children receiving tablets (see Pharmacokinetic properties).

3TC ORAL SOLUTION given concomitantly with other antiretroviral oral solutions should be used for the treatment of HIV infection only when the benefits of treatment outweigh possible risks including lower virological suppression.

Effects on ability to drive and use machines: No adverse effects regarding the patient's ability to drive or operate machinery have been observed.

Oral Solution: Contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take 3TC ORAL SOLUTION.

INTERACTIONS:

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

3TC is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicines administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic transport system e.g. trimethoprim. Other active substances (e.g. ranitidine, cimetidine) are eliminated only in part by the mechanism and were shown not to interact with lamivudine.

Zidovudine: A modest increase in C_{max} (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered when co-administered with 3TC. Zidovudine has no effect on the pharmacokinetics of lamivudine.

Zalcitabine: 3TC may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. 3TC is therefore not recommended to be used in combination with zalcitabine.

Trimethoprim/sulphamethoxazole: Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40 % increase in 3TC exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of 3TC is necessary (see DOSAGE AND DIRECTIONS FOR USE). 3TC has no effect on the pharmacokinetics of co-trimoxazole. The effect of co-administration of 3TC with higher doses of co-trimoxazole for the treatment of *Pneumocystis carinii* pneumonia and toxoplasmosis has not been studied.

Emtricitabine: Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicines are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these medicines in combination therapy may be limited. 3TC is not recommended for use in combination with emtricitabine.

PREGNANCY AND LACTATION:

Pregnancy: There are no adequate and well-controlled trials in pregnant women and the safe use of lamivudine in human pregnancy has not been established.

Consistent with passive transmission of the medicine across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum

at delivery. Reproductive studies in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. There was some evidence of early embryolethality when administered to pregnant rabbits at exposure levels comparable to those achieved in information on placental transfer in humans.

There have been reports of mild and transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of elevations in serum lactate is unknown. There have also been reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and 3TC exposure *in utero* or peri-partum has not been established.

Lactation: A study in lactating rats showed that, following oral administration, lamivudine was excreted in breast milk. Lamivudine is excreted in human breast milk at similar concentrations to those found in serum. Since the medicine may pass into breast milk, mothers taking 3TC should not breastfeed their infants**.**

DOSAGE AND DIRECTIONS FOR USE:

3TC can be taken with food or without food.

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing. 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.

The package insert for zidovudine must be consulted for information on its dosage and administration.

Adults, adolescents and children weighing at least 25 kg:

Oral solution:

The recommended dose of lamivudine is 300 mg (30 ml) daily. This may be administered as 300 mg (30 ml) once daily or 150 mg (15 ml) twice daily.

Tablets:

The recommended dose of lamivudine is 300 mg daily. This may be administered as either 300 mg (two 150 mg tablets), once daily or 150 mg (one 150 mg tablet) twice daily.

Children

***Children < 3 months of age*:**

The limited data available are insufficient to propose specific dosage recommendations (see Pharmacokinetic properties).

Oral Solution:

***For Children aged ≥ 3 months and weighing less than 25 kg*:**

The recommended dose is 4 mg/kg twice daily or 8 mg/kg once daily up to a maximum of 300 mg daily.

See WARNINGS AND SPECIAL PRECAUTIONS.

Tablets:

Children weighing between 14 kg to < 20 kg:

The recommended total daily dose of lamivudine is 150 mg. This may be administered as either one-half of a scored tablet twice daily or one whole tablet once daily.

Children weighing ≥ 20 kg to < 25 kg:

The recommended total daily dose of lamivudine is 225 mg. This may be administered as either one-half of a scored tablet in the morning and one whole tablet in the evening, or one and a half scored tablets once daily.

Children weighing at least 25 kg:

The adult dosage of 150 mg twice daily or 300 mg once daily should be taken.

Renal Impairment:

Lamivudine concentrations are increased in patients with moderate to severe renal impairment due to decreased clearance. The doses should therefore be reduced for patients with a creatinine clearance of less than 50 ml/min as shown in the table below. The same percentage reduction in dose applies for paediatric patients with renal impairment.

When doses below 150 mg are needed the use of the oral solution is recommended.

Adults, adolescents and children weighing at least 25 kg:

Creatinine Clearance (ml/min)	**Recommended dose of 3TC**
≥ 50	150 mg twice daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily
5-14	150 mg first dose, then 50 mg once daily
< 5	50 mg first dose, then 25 mg once daily

Children ≥ 3 months and weighing less than 25 kg:

Creatinine Clearance (ml/min)	**Recommended dose of 3TC**
≥ 50	4 mg/kg first dose, then 4 mg/kg twice daily
30-49	4 mg/kg first dose, then 4 mg/kg once daily
15-29	4 mg/kg first dose, then 2,6 mg/kg once daily
5-14	4 mg/kg first dose, then 1,3 mg/kg once daily
< 5	1,3 mg/kg first dose, then 0,7 mg/kg once daily

Hepatic Impairment:

No dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

SIDE EFFECTS:

The following events have been reported during therapy for HIV disease with 3TC alone and in combination with zidovudine.

The following convention has been utilised for the classification of undesirable effects:

Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000), very rare (< 1/10 000).

Blood and lymphatic system disorders:

Uncommon: neutropenia, anaemia, thrombocytopenia

Very rare: pure red cell aplasia

Metabolism and nutrition disorders:

Common: hyperlactataemia

Rare: lactic acidosis (see WARNINGS AND SPECIAL PRECAUTIONS).

Lipodystrophy (redistribution/accumulation of body fat (see WARNINGS AND SPECIAL PRECAUTIONS)).

Nervous system disorders:

Common: headache

Very rare: paraesthesia, peripheral neuropathy

Gastrointestinal disorders:

Common: nausea, vomiting, upper abdominal pain, diarrhoea

Rare: pancreatitis, rises in serum amylase

Hepatobiliary disorders:

Uncommon: transient rises in liver enzymes (AST, ALT)

Skin and subcutaneous tissue disorders:

Common: rash, alopecia

Musculoskeletal and connective tissue disorders:

Common: arthralgia, muscle disorders

Rare: rhabdomyolysis

General disorders and administration site conditions:

Common: fatigue, malaise, fever.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No specific signs or symptoms have been identified.

If overdosage occurs, the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

IDENTIFICATION:

3TC TABLETS:

White film-coated, diamond shaped scored tablets engraved ‘GXCJ7’ on both faces.

3TC ORAL SOLUTION:

A clear, colourless to pale yellow solution with the odour of fruit.

PRESENTATION:

3TC TABLETS are supplied in cartons containing 60 tablets in a white high density polyethylene (HDPE) bottle, with a child-resistant cap.

3TC ORAL SOLUTION is supplied in cartons containing a white polyethylene bottle, with a child-resistant cap and dosing device. The bottle contains 240 ml (10 mg/ml) of lamivudine solution for oral use only.

STORAGE INSTRUCTIONS:

3TC TABLETS: Store at or below 30 °C.

3TC ORAL SOLUTION: Store at or below 25 °C.

Discard oral solution one month after first opening.

Keep out of reach of children.

REGISTRATION NUMBER:

3TC TABLETS: 30/20.2.8/0366

3TC ORAL SOLUTION: 30/20.2.8/0367

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration:

3TC TABLETS: 13 June 1996

3TC ORAL SOLUTION: 13 June 1996

Date of most recent revision:

29 June 2018

GDS21

446

447 History:

448 Amended: 11 August 2003, APPROVED: 05/09/2003 Registration of 300 mg tablet
449 Amended: May 2003 Address change to Bryanston (Notification)
450 Amended: 04 November 2003 (To include the preferential access pack; correct
451 presentation of 150 mg to comply with Ann 8, correction of preservatives to comply with
452 Ann 2) – permitted amendment.
453 Amended: 21 May 2005 (Access Pack tablet colour change) Resubmitted: 17 January
454 2005 as per MCC request.
455 Amended: 07 June 2004 (In-line with GCT versions 5 – 8); 12 May 2005 (Response to
456 CC Recommendations 04/03/05); 02 September 2005 (In-line with CC
457 Recommendations 19/08/2005)
458 Amended: 28 January 2008 (Change in tablet identification) – immediate implementation
459 Amended: 26 May 2008 (Inclusion of paediatric dosing + safety update: GDS versions 9
460 to 13)
461 Amended: 09 October 2008 (response to CCC recommendations 04/09/02) – compliant.
462 Approved 17/04/2009
463 Amended: 19 April 2011 (Applicant address change)
464 GDS14 & 15: Submitted 10.02.2011
465 Notification of Regulation 9 & 10 implementation: Submitted 05 November 2015
466 GDS14-21: Resubmission of 14-15, including new safety: 12 November 2015, CCCR
467 dated 23.06.2016.
468 GSK response: 06.10.2016, CCCR dated 23.06.2017
469 GSK response: 08.08.2017, Approved: 29.06.2018
470