Appendix 1: List of contraindications to propranolol and/or etodolac:

- Known allergy or hypersensitivity to propranolol and/or etodolac and/or any other ingredient of the used brands
- History or evidence of significant cardiac disease: congestive or severe heart failure; New York Heart Association class ≥ 2; active coronary artery disease; unstable angina, cardiac arrhythmias requiring anti-arrhythmic therapy, uncontrolled hypertension, patients with recent (less than 6 months) myocardial infarction or coronary re-vascularization; cardiogenic shock; sick sinus syndrome; sinoatrial block; acidosis
- Hypotension at the time of screening (i.e., systolic blood pressure < 100 mmHg. Diastolic blood pressure < 60 mmHg)
- Symptomatic bradycardia or resting heart rate < 50 bpm at time of screening
- Bronchial hyperresponsiveness, including active chronic asthma
- Active peptic ulcer disease or gastrointestinal bleeding
- Decompensated diabetes mellitus (repeated measurements of glucose > 300 mg/dl despite usual medical treatment, (keto-) acidosis, exsiccosis due to decompensated diabetes)
- Chronic inflammatory bowel disease (M. Crohn or Ulcerative colitis)
- Severe peripheral vascular disease
- Concurrent use of monoaminooxidase inhibitor (excluding monoaminooxidase-B inhibitor)
- Intravenous application of calcium channel blockers (non-dihydropyridine) and other antiarrhythmic agents
- Severe thrombocytopenia
- Sensitivity to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) in terms of asthma, urticarial or acute rhinitis
- Chronic use of any beta-adrenergic blocker within the last 3 months
- Chronic use of any cyclooxygenase (COX) inhibitor within the last 3 months
- Participation in another interventional trial
- Pharmaceutical preparations with which major interactions can be expected by propranolol and/or etodolac in patients' long-term therapy*
- Diseases or findings that may have a significant effect on the target variables and which may therefore mask or inhibit the therapeutic effect under investigation
- Persons with any kind of dependency on the investigator or employed by the sponsor or investigator
- Persons held in an institution by legal or official order; legally incapacitated patients
- Persons with understanding/language problems or inability to comply with study and/or follow-up procedures
- Any condition which could result in an undue risk for the patient and/or influence out-come measures in the opinion of the investigator

*see Appendix 2 for possible interactions

Appendix 2: Possible major interactions with patient's concomitant medication

A) Etodolac:

Severity: Major
Risk rating: Avoid combination

- NSAIDs and selective COX-2 inhibitors may enhance the adverse/toxic effect of Etodolac.
- Etodolac (as a photosensitizing agent) may enhance the photosensitizing effect of Aminolevulinic Acid (5-ALA). Avoid administration of other photosensitizing agents within 24 hours before or 24 hours after orally administered 5-ALA. As 5-ALA is administered for visualization of malignant tissue in glioma patient, it is unlikely that study participant experience this kind of interaction.
- Etodolac may enhance the anticoagulant effect of Urokinase.

Severity: Major
Risk rating: Consider therapy modification

- Etodolac may enhance the adverse/toxic effect of Apixaban, Rivaroxaban, Dabigatran Etexilate, Edoxaban. Specifically, the risk of bleeding may be increased. If combined, monitor patients extra closely for signs and symptoms of bleeding with any concurrent use, and counsel patients about the increased risk of bleeding and the need to promptly report any signs or symptoms of possible bleeding.
- Monitor for decreased serum concentrations/therapeutic effects Etodolac if coadministered with bile acid sequestrants (Cholestyramine Resin). Separating the administration of doses by 2 or more hours may reduce (but not eliminate) the risk of interaction.
- Etodolac may enhance the nephrotoxic effect of Cyclosporine. Monitor for evidence of nephrotoxicity, as well as increased serum cyclosporine concentrations and systemic effects (e.g. hypertension) during concomitant therapy.
- Etodolac may increase the serum concentration of Lithium. Consider reducing the dosage of lithium upon initiation of Etodolac. Monitor for increased therapeutic/toxic effects of lithium if Etodolac is initiated/dose increased, or decreased effects if Etodolac is discontinued/dose decreased.
- Etodolac may increase the serum concentration of Methotrexate. If methotrexate and Etodolac are to be used concomitantly, monitor patients for evidence of hematologic toxicity (frequent complete blood count), nephrotoxicity (frequent serum creatinine), and hepatotoxicity (liver function tests).
- Etodolac may enhance the adverse/toxic effect of Salicylates (excluding low dose acetyl-salicylic acid, e.g. aspirin 100 mg/day).
- Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of Etodolac. Etodolac may diminish the therapeutic effect of Selective Serotonin Reuptake Inhibitors. To minimize the risk of bleeding associated with this combination, consider using alternative analgesics, when appropriate, and/or addition of a gastroprotective agent, such as a proton pump inhibitor for the time that combined therapy is necessary.
- Sodium Phosphates may enhance the nephrotoxic effect of Etodolac. Specifically, the risk of acute phosphate nephropathy may be enhanced. This interaction has only been demonstrated with large oral sodium phosphate doses used for bowel preparation (typically greater than 20 g).
- Etodolac may enhance the nephrotoxic effect of Tenofovir Products. Avoid concurrent use of tenofovir with high-dose of Etodolac when possible due to a potential risk for acute renal failure. This risk has been most clearly shown with the NSAID diclofenac, but some data suggest that other NSAIDs may also be capable of interacting with tenofovir.
- Etodolac may enhance the anticoagulant effect of Vitamin K Antagonists (Acenocoumarol, Phenindione, Warfarin). Monitor for increased signs and symptoms of bleeding.

B) Propranolol:

Severity: Major
Risk rating: Avoid combination

- Propranolol may diminish the bronchodilatory effect of Beta-2-Agonists (Bambuterol, Fenoterol, Formoterol, Indacaterol, Levosalbutamol, Olodaterol, Orciprenalin, Salbutamol, Salmeterol, Terbutaline, Vilanterol).

- Bradycardia-Causing Agents may enhance the bradycardic effect of Ceritinib. Avoid concurrent use of ceritinib with propranolol when possible. If such use cannot be avoided, monitor patients for evidence of symptomatic bradycardia, and closely monitor blood pressure and heart rate during therapy. Adjustment of ceritinib therapy (i.e., dose reduction and/or temporary discontinuation) may be necessary for symptomatic bradycardia.
- Propranolol may enhance the adverse/toxic effect of Methacholine. Methacholine administration is contraindicated in patients receiving any beta-blocker.
- Rivastigmine may enhance the bradycardic effect of propranolol. Due to the risk of additive bradycardic effects, including syncope, the concomitant use of rivastigmine and beta-blockers is not recommended.

Severity: Major
Risk rating: Consider therapy modification

- Abiraterone Acetate may increase the serum concentration of propranolol (as a CYP2D6 substrate). When concurrent use is not avoidable, monitor patients closely for signs/symptoms of propranolol toxicity.
- CYP2D6 inhibitors: Fluoxetine, Paroxetine, Quinidine, Tipranavir may decrease the metabolism of propranolol. Consider an alternative for one of the interacting drugs in order to avoid toxicity of propranolol. Some combinations are specifically contraindicated by manufacturers. Suggested dosage adjustments are also offered by some manufacturers. Please review applicable package inserts. Monitor for increased effects of propranolol if a cytochrome P (CYP) inhibitor is initiated/dose increased, and decreased effects if a CYP inhibitor is discontinued/dose decreased.
- Dronedarone may enhance the bradycardic effect of propranolol and increase the serum concentration of propranolol.
- Fluvoxamine (as a CYP1A2 inhibitor) may increase effects of propranolol is initiated/dose increased, and decrease effects if fluvoxamine is discontinued/dose decreased.
- Propranolol may enhance the vasopressor effect of direct-acting Alpha-/Beta-Agonists (Dopamine, Ephedrine (Nasal), Ephedrine (Systemic), Epinephrine (Nasal), Epinephrine (Oral Inhalation), Epinephrine (Systemic), Isometheptene, Levonordefrin, Metaraminol, Norepinephrine). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. Some beta-adrenoceptor mediated effects of Alpha-/Beta-Agonists (Direct-Acting), including anti-anaphylactic effects of epinephrine, may be diminished by Beta-Blockers. Monitor for increases in pressor effects of alpha-/beta-agonists if used in patients receiving propranolol. Beta-1-selective (i.e., “cardioselective”) agents may confer a more limited risk if used in low enough doses to allow them to retain their selectivity. Infiltrating larger volumes of local anesthetics for other surgical procedures (e.g., more than 0.06mg epinephrine) may cause clinically-relevant problems. Patients with allergies that require carrying and periodically using subcutaneous epinephrine (e.g. bee sting kits) should probably avoid the use of propranolol.
- Alpha-2-Agonists (Brimonidine (Ophthalmic), Clonidine, Dexmedetomidine, Guanfacine, Lofexidine, Methyldopa, Moxonidine, Rilmenidine, Tizanidine, Excep-tion: Apraclonidine) may enhance the atrio-ventricular-blocking (AV-block) effect of propranolol. Sinus node dysfunction may also be enhanced. Propranolol may enhance the re-bound hypertensive effect of Alpha-2-Agonists. This effect can occur when the Alpha-2-Agonist is abruptly withdrawn.
- Propranolol may enhance the hypotensive effect of Amifostine. Amifostine should not be administered when propranolol is concomitantly used.
- Propranolol may enhance the vasoconstricting effect of Ergot Derivatives (Bromocriptine, Cabergoline, Dihydroergotamine, Ergoloid Mesylates, Ergonovine, Ergotamine, Methylergonovine, Pergolide, Exception: Nicergoline). Consider alternatives whenever possible in order to avoid this combination. If concurrent use cannot be avoided, monitor patients closely for evidence of excessive peripheral vasoconstriction.
- Beta-Blockers may enhance the bradycardic effect of Fingolimod. Avoid the concomitant use of fingolimod and beta-blockers if possible. If co-administration is necessary, patients should have overnight continuous electrocardiogram monitoring conducted after the first dose of fingolimod. Closely monitor patients for the development of bradycardia and other serious arrhythmias.
- Obinutuzumab may enhance the hypotensive effect of propranolol. In order to minimize the risk of excessive hypotension during or immediately after obinutuzumab infusion, clinicians

should consider temporarily withholding propranolol beginning 12 hours prior to infusion and continuing until 1 hour after infusion and until the patient's blood pressure is stable.

- Panobinostat may increase the serum concentration of propranolol. Avoid concurrent use of propranolol when possible. If such a combination cannot be avoided, monitor patients closely for evidence of propranolol toxicity.
- Propranolol may increase the serum concentration of Rizatriptan. Rizatriptan dose should be reduced to 5mg in patients who are also being treated with propranolol. Monitor clinical response to rizatriptan closely with use of this combination.
- Propranolol may diminish the bronchodilatory effect of Theophylline Derivatives (Acebrophylline, Aminophylline, Dyphylline, Theophylline). Consider avoiding the concomitant use of propranolol and theophylline derivatives. If concomitant use cannot be avoided, monitor for symptoms of reduced theophylline efficacy.
- Propranolol may increase the serum concentration of Tizanidine. Avoid the use of tizanidine with propranolol when possible. If combined use cannot be avoided, initiate tizanidine at an adult dose of 2 mg and increase in 2 to 4 mg increments based on patient response. Monitor for increased effects of tizanidine, including adverse reactions (e.g. hypotension, bradycardia, drowsiness).
- Vemurafenib may increase the serum concentration of propranolol. Consider alternatives to such combinations whenever possible.