Gefitinib: Drug information

(For additional information see "Gefitinib: Patient drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

Iressa

Brand Names: Canada

IRESSA

Pharmacologic Category

Antineoplastic Agent, Epidermal Growth Factor Receptor (EGFR) Inhibitor; Antineoplastic Agent, Tyrosine Kinase Inhibitor

Dosing: Adult

Non-small cell lung cancer (NSCLC), metastatic, with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations: Oral: 250 mg once daily until disease progression or unacceptable toxicity.

NSCLC, locally advanced or metastatic with EGFR mutations (Canadian labeling): Oral: 250 mg once daily.

Missed doses: Do not take a missed dose if it is within 12 hours of the next scheduled dose.

Dosage adjustment for concomitant therapy (US labeling): *Strong CYP3A4 inducers (eg, phenytoin, rifampin, or tricyclic antidepressants):* Increase gefitinib to 500 mg once daily (in the absence of severe adverse drug reactions); reduce gefitinib dose back to 250 mg once daily 7 days after discontinuing the strong CYP3A4 inducer.

Dosing: Pediatric

Non-small cell lung cancer (NSCLC), locally advanced or metastatic with EGFR mutations (Canadian labeling): Adolescents ≥17 years: Oral: Refer to Canadian adult dosing.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

US labeling: There are no dosage adjustments provided in the manufacturer's labeling; however, due to minimal renal excretion (<4% of gefitinib and metabolites) the need for dosage adjustment is unlikely. Use has not been studied in patients with CrCl ≤20 mL/minute.

Canadian labeling: No dosage adjustment necessary. Use caution in severe impairment (CrCl ≤20 mL/minute).

Dosing: Hepatic Impairment

Dosage adjustment for hepatic impairment at treatment initiation:

US labeling: There are no dosage adjustments provided in the manufacturer's labeling; systemic exposure is increased in hepatic impairment.

Canadian labeling: No dosage adjustment necessary. Use caution in moderate to severe impairment (Child-Pugh Class B or C) (systemic exposure may be increased); monitor closely.

Dosage adjustment for hepatotoxicity during treatment:

ALT and/or AST elevations (grade 2 or higher): Withhold treatment for up to 14 days; may resume treatment when fully resolved or improved to grade 1.

Severe hepatic impairment: Permanently discontinue.

Dosing: Adjustment for Toxicity

Dermatologic toxicity:

Skin reactions (grade 3 or higher): Withhold treatment for up to 14 days; may resume treatment when fully resolved or improved to grade 1. *Canadian labeling:* Discontinue if unable to tolerate rechallenge following treatment interruption.

Severe bullous, blistering or exfoliating dermatologic conditions: Interrupt or discontinue treatment.

Gastrointestinal toxicity:

Diarrhea (grade 3 or higher): Withhold treatment for up to 14 days; may resume treatment when fully resolved or improved to grade 1. *Canadian labeling:* Discontinue if unable to tolerate rechallenge following treatment interruption.

Gastrointestinal perforation: Permanently discontinue.

Ocular toxicity:

Signs/symptoms of severe or worsening disorders, including keratitis: Withhold treatment for up to 14 days; may resume treatment when fully resolved or improved to grade 1. *Canadian labeling:* Discontinue if unable to tolerate rechallenge following treatment interruption.

Persistent ulcerative keratitis: Permanently discontinue.

Pulmonary toxicity:

Acute onset or worsening symptoms (dyspnea, cough, fever): Withhold treatment for up to 14 days; may resume treatment when fully resolved or improved to grade 1.

Interstitial lung disease (ILD), confirmed: Permanently discontinue.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Iressa: 250 mg

Generic Equivalent Available (US) No

Dosage Forms: Canada Information with regard to form, strength, and availability of products uniquely available in Canada but currently not available in the US. Refer also to Dosage forms.

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, oral:

Iressa: 250 mg

Administration Oral: Administer with or without food.

For patients unable to swallow the tablet whole, place tablet in 120 to 240 mL water and stir for ~15 minutes; immediately drink the liquid or administer through a naso-gastric tube. Rinse the container with 120 to 240 mL water and immediately drink or administer through naso-gastric tube.

Hazardous Drugs Handling Considerations

Hazardous agent (meets NIOSH 2016 criteria). This medication is not on the NIOSH (2016) list; however, it meets the criteria for a hazardous drug. Drugs are classified as hazardous based on their properties; the properties of a hazardous drug include one or more of the following characteristics: carcinogenic, teratogenic (or other developmental toxicity), reproductive toxicity, organotoxic at low doses, genotoxic, and/or new agents with structural or toxicity profiles similar to existing hazardous agents.

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends single gloving for administration of intact tablets or capsules. If manipulating tablets/capsules (eg, to prepare an oral suspension), NIOSH recommends double gloving, a protective gown, and preparation in a controlled device; if not prepared in a controlled device, respiratory and eye/face protection as well as ventilated engineering controls are recommended. NIOSH recommends double gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid/feeding tube administration (NIOSH 2016).

Use

Non-small cell lung cancer:

US labeling: First-line treatment of metastatic non-small cell lung cancer (NSCLC) in tumors with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an approved test.

Limitation of use: Safety and efficacy have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations

Canadian labeling: First-line treatment of locally advanced (nonresponsive to curative therapy) or metastatic NSCLC with activating mutations of the epidermal growth factor receptor tyrosine kinase (EGFR-TK).

Medication Safety Issues

Sound-alike/look-alike issues:

Gefitinib may be confused with afatinib, axitinib, crizotinib, erlotinib, imatinib, SORAfenib, SUNItinib, vandetanib

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

>10%:

Central nervous system: Insomnia (15%), fatigue (14%)

Dermatologic: Dermatological reaction (47% to 58%), skin rash (52%), xeroderma (24%), pruritus (18%), paronychia (14%), acne vulgaris (11%), alopecia (5% to 11%)

Gastrointestinal: Diarrhea (29% to 47%; grades 3/4: 3%), anorexia (19% to 20%), nausea (17% to 18%), decreased appetite (17%), vomiting (13% to 14%), stomatitis (7% to 13%), constipation (12%)

Genitourinary: Proteinuria (8% to 35%)

Hepatic: Increased serum AST (8% to 40%; grades 3/4: 2% to 3%), increased serum ALT (11% to 38%; grades 3/4: 2% to 5%)

Neuromuscular & skeletal: Weakness (18%)

1% to 10%:

Central nervous system: Hypoesthesia (4%), peripheral sensory neuropathy (4%), peripheral neuropathy (2%)

Dermatologic: Nail disease (5% to 8%), acneiform eruption (6%)

Endocrine & metabolic: Dehydration (2%; secondary to diarrhea, nausea, vomiting, or anorexia)

Gastrointestinal: Xerostomia (2%)

Genitourinary: Cystitis (1%)

Hematologic & oncologic: Anemia (7%), pulmonary hemorrhage (4% to 5%), hemorrhage (4%; including epistaxis, hematuria), neutropenia (3%), leukopenia (2%), thrombocytopenia (1%)

Hepatic: Increased serum bilirubin (3%; grades 3/4: <1%)

Neuromuscular & skeletal: Myalgia (8%), arthralgia (6%)

Ophthalmic: Eye disease (6% to 7%; grades 3/4: <1%; including conjunctivitis, blepharitis, and dry eye)

Renal: Increased serum creatinine (2%)

Respiratory: Cough (9%), interstitial pulmonary disease (1%; grades 3/4: 3%)

Miscellaneous: Fever (9%)

<1%, postmarketing, and/or case reports: Angioedema, bullous skin disease, corneal erosion (reversible; may be associated with aberrant eyelash growth), decreased white blood cell count, erythema multiforme, fulminant hepatitis, gastrointestinal perforation, hemorrhagic cystitis, hepatic failure, hepatitis, hypersensitivity angiitis, hypersensitivity reaction, keratitis, keratoconjunctivitis sicca, pancreatitis, renal failure, skin fissure, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Hypersensitivity to gefitinib or any component of the formulation.

Warnings/Precautions

Concerns related to adverse effects:

• Dermatologic toxicity: Skin reactions occurred in nearly one-half of patients taking gefitinib. Bullous skin disorders, including toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, and dermatitis bullous have been reported. Interrupt gefitinib treatment or discontinue for development of severe bullous, blistering, or exfoliating dermatologic conditions.

• Gastrointestinal effects: Diarrhea occurs in approximately one-third of patients; grade 3 or 4 diarrhea has been observed. Diarrhea symptoms should be managed as clinically indicated; avoid dehydration. Withhold gefitinib for severe or persistent (up to 14 days) diarrhea. Gastrointestinal perforation has occurred (rarely); discontinue permanently if gastrointestinal perforation develops. Nausea, vomiting, decreased appetite, and stomatitis have also been reported.

• Hepatotoxicity: Increases in ALT, AST, and bilirubin, including grade 3 or higher toxicity have been observed. Fatal hepatotoxicity has occurred rarely. Monitor liver functions tests periodically. Withhold gefitinib in patients with worsening liver function; discontinue for severe hepatic impairment.

• Ocular toxicity: Ocular disorders, including keratitis, corneal erosion, abnormal eyelash growth, conjunctivitis, blepharitis, and dry eye have been reported; some events were grade 3. Recent corneal surgery and contact lens wearing may be risk factors for ocular toxicity. Advise patients to promptly report developing eye symptoms and promptly refer for ophthalmic evaluation if signs of keratitis (eg, acute or worsening of eye inflammation, lacrimation, blurred vision, pain, red eye, and/or light sensitivity). Interrupt gefitinib treatment or discontinue for severe or worsening ocular disorders.

• Pulmonary toxicity: Interstitial lung disease (ILD) or ILD-like reactions (eg, acute respiratory distress syndrome, lung infiltration, pneumonitis, or pulmonary fibrosis) have occurred (rarely) with gefitinib; some cases were grade 3 or higher and some were fatal. Withhold gefitinib and promptly assess any patient with worsening respiratory symptoms (dyspnea, cough, and fever); discontinue permanently if ILD is confirmed. Increased systemic gefitinib exposure is associated with an increased incidence of ILD. An increase in mortality was observed in patients with the following risk factors: Smoking, CT scan evidence of reduced normal lung (≤50%), preexisting ILD, increased age (≥65 years), and extensive areas adherent to pleura (≥50%).

Disease-related concerns:

• Hepatic impairment: Gefitinib exposure is increased in patients with mild, moderate, and severe hepatic impairment due to cirrhosis. However, in a study of patients with liver metastases, patients with metastases and moderate impairment had similar systemic exposure as patients with metastases and normal hepatic function. Monitor for adverse reactions if administering to patients with moderate or severe hepatic impairment.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

• Drugs that affect gastric pH: Elevated gastric pH may reduce gefitinib plasma concentrations; if possible, avoid concomitant use with proton pump inhibitors. If proton pump inhibitor therapy is necessary, administer gefitinib 12 hours before or 12 hours after the proton pump inhibitor dose. May administer gefitinib 6 hours before or 6 hours after H_2-receptor antagonists or antacids.

Special populations:

• CYP2D6 poor metabolizers: Systemic exposure of gefitinib may be increased in CYP2D6 poor metabolizers. No dosage adjustment is recommended, although patients should be monitored closely for adverse reactions.

Dosage form specific issues:

• Lactose: May contain lactose; consider intolerance risk in patients with galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

Other warnings/precautions:

• Appropriate use: Establish EGFR mutation status prior to treatment. Do not use in patients with EGFR mutation-negative tumors. Studies have demonstrated a subset of patients who are more likely to respond to gefitinib treatment. This subset includes patients of Asian origin, never-smokers, women, patients with bronchoalveolar adenocarcinoma, and patients with EGFR-mutated tumors. Deletion in exon 19 and mutation in exon 21 are the two most commonly found EGFR mutations; both mutations correlate with clinical response, resulting in increased response rates in patients with the mutation (Riely, 2006). Studies have compared gefitinib in treatment naïve patients to combination chemotherapy in the subsets of patients described above, resulting in a longer progression free survival in the gefitinib arm (Mok 2009). ASCO guidelines state that the first-line use of gefitinib may be recommended in stage IV disease with activating EGFR mutations (Masters 2015). In patients with a KRAS mutation, however, EGFR-TKI therapy is not recommended.

Metabolism/Transport Effects

Substrate of BCRP, CYP2D6 (major), CYP3A4 (major); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** BCRP, CYP2D6 (weak)

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Abiraterone Acetate: May increase the serum concentration of CYP2D6 Substrates. Management: Avoid concurrent use of abiraterone with CYP2D6 substrates that have a narrow therapeutic index whenever possible. When concurrent use is not avoidable, monitor patients closely for signs/symptoms of toxicity. *Risk D: Consider therapy modification*

Ajmaline: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of Gefitinib. Management: Administer gefitinib at least 6 hours before or after administration of an antacid, and closely monitor clinical response to gefitinib. *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

ARIPiprazole: CYP2D6 Inhibitors (Weak) may increase the serum concentration of ARIPiprazole. Management: Monitor for increased aripiprazole pharmacologic effects. Aripiprazole dose adjustments may or may not be required based on concomitant therapy and/or indication. Consult full interaction monograph for specific recommendations. *Risk C: Monitor therapy*

Asunaprevir: May increase the serum concentration of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ceritinib: May increase the serum concentration of CYP3A4 Substrates. Management: Use of ceritinib with a narrow therapeutic index CYP3A substrate (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) should be avoided when possible. *Risk C: Monitor therapy*

Cobicistat: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Gefitinib. Management: In the absence of severe adverse reactions, increase gefitinib dose to 500 mg daily in patients receiving strong CYP3A4 inducers; resume 250 mg dose 7 days after discontinuation of the strong inducer. Carefully monitor clinical response. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Gefitinib. *Risk C: Monitor therapy*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Enzalutamide: May decrease the serum concentration of CYP3A4 Substrates. Management: Concurrent use of enzalutamide with CYP3A4 substrates that have a narrow therapeutic index should be avoided. Use of enzalutamide and any other CYP3A4 substrate should be performed with caution and close monitoring. *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

H2-Antagonists: May decrease the serum concentration of Gefitinib. Management: Administer gefitinib at least 6 hours before or after administration of a histamine H2-antagonist, and closely monitor clinical response to gefitinib. *Risk D: Consider therapy modification*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Imatinib: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Lumefantrine: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

MiFEPRIStone: May increase the serum concentration of CYP3A4 Substrates. Management: Minimize doses of CYP3A4 substrates, and monitor for increased concentrations/toxicity, during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. *Risk D: Consider therapy modification*

Mitotane: May decrease the serum concentration of CYP3A4 Substrates. Management: Doses of CYP3A4 substrates may need to be adjusted substantially when used in patients being treated with mitotane. *Risk D: Consider therapy modification*

Netupitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Panobinostat: May increase the serum concentration of CYP2D6 Substrates. Management: Avoid concurrent use of sensitive CYP2D6 substrates when possible, particularly those substrates with a narrow therapeutic index. *Risk D: Consider therapy modification*

Peginterferon Alfa-2b: May decrease the serum concentration of CYP2D6 Substrates. Peginterferon Alfa-2b may increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Perhexiline: CYP2D6 Inhibitors (Weak) may increase the serum concentration of Perhexiline. *Risk C: Monitor therapy*

Perhexiline: CYP2D6 Substrates may increase the serum concentration of Perhexiline. Perhexiline may increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Proton Pump Inhibitors: May decrease the serum concentration of Gefitinib. Management: Avoid use of proton pump inhibitors (PPIs) with gefitinib when possible. If required, administer gefitinib 12 hours after administration of the PPI or 12 hours before the next dose of the PPI. *Risk D: Consider therapy modification*

QuiNINE: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Simeprevir: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

St John's Wort: May decrease the serum concentration of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. *Risk D: Consider therapy modification*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Vinorelbine: Gefitinib may enhance the neutropenic effect of Vinorelbine. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Gefitinib may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Food Interactions Grapefruit juice may increase serum gefitinib concentrations. Management: Avoid concurrent use.

Pregnancy Implications Adverse events have been observed in animal reproduction studies. Gefitinib may cause fetal harm when administered to a pregnant woman. Women of reproductive potential should use effective contraception during and for at least 2 weeks following gefitinib treatment.

Breast-Feeding Considerations It is not known if gefitinib is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended by the manufacturer.

Monitoring Parameters EGFR mutation status (prior to treatment initiation); liver function tests (ALT, AST, bilirubin at baseline and periodically thereafter); BUN, creatinine, and electrolytes (baseline and periodically thereafter); INR or prothrombin time (with concurrent warfarin treatment). Monitor for signs/symptoms of dermatologic toxicity, gastrointestinal perforation, ocular toxicity, and pulmonary toxicity; monitor closely for adverse reactions in CYP2D6 poor metabolizers and patients with hepatic impairment.

Mechanism of Action Gefitinib is a tyrosine kinase inhibitor (TKI) which reversibly inhibits kinase

activity of wild-type and select activation mutations of epidermal growth factor receptor (EGFR). EGFR is expressed on cell surfaces of normal and cancer cells and has a role in cell growth and proliferation. Gefitinib prevents autophosphorylation of tyrosine residues associated with the EGFR receptor, which blocks downstream signaling and EGFR-dependent proliferation. Gefitinib has a higher binding affinity for EGFR exon 19 deletion and exon 21 (L858R) substitution mutation than for wild-type EGFR.

Pharmacodynamics/Kinetics

Absorption: Oral: Slow

Distribution: 1400 L

Protein binding: 90%, albumin and alpha$_1$-acid glycoprotein

Metabolism: Hepatic (extensive), primarily via CYP3A4, as well as CYP2D6; forms metabolites

Bioavailability: 60%

Half-life elimination: Oral: 41 hours

Time to peak, plasma: Oral: 3 to 7 hours

Excretion: Feces (86%); urine (<4%)

Pricing: US

Tablets (Iressa Oral)

250 mg (30): $9117.36

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Gefticip (LK); Geftilon (IN); Iressa (AE, AR, AT, AU, BE, BH, BR, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EE, ES, FR, GB, GR, GT, HK, HN, HR, ID, IE, IL, IS, JO, KR, KW, LB, LK, LT, LU, LV, MT, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, QA, RO, RU, SE, SG, SI, SK, SV, TH, TR, TW, VE, VN)

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Topic 8712 Version 134.0