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Alitretinoin*

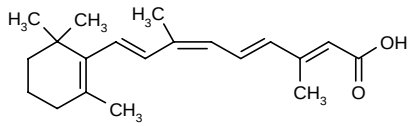
Prop INN; USAN

Retinoid
Treatment of Chronic Hand Dermatitis

BAL-4079

9-*cis*-Retinoic acid
(2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid

InChI=1/C20H28O2/c1-15(8-6-9-16(2)14-19(21)22)11-12-18-17(3)10-7-13-20(18,4)5/h6,8-9,11-12,14H,7,10,13H2,1-5H3,(H,21,22)/b9-6+,12-11+,15-8-,16-14+



$C_{20}H_{28}O_2$
Mol wt: 300.4351

CAS: 005300-03-8

EN: 213594

Abstract

Alitretinoin is an endogenous retinoid that activates all known intracellular retinoid receptor subtypes (RARα, RARβ, RARγ, RXRα, RXRβ and RXRγ). Alitretinoin is currently approved as a 0.1% gel for the treatment of cutaneous Kaposi's sarcoma. Although alitretinoin has been investigated as an oral treatment for Kaposi's sarcoma (and other neoplasms) and was shown to be somewhat effective in this regard, it has not been approved for this indication in the United States, Japan or the European Union. However, a successful phase III trial was carried out with oral alitretinoin for the treatment of chronic hand dermatitis (eczema) in the E.U. If approved, alitretinoin would be the first oral therapy specifically indicated for chronic hand dermatitis.

Synthesis+

Alitretinoin can be obtained by the following synthetic strategies. The photoisomerization of *trans*-retinoic acid (I) in hot acetonitrile using a tungsten lamp produces an equilibrium mixture containing the target 9-*cis*-retinoic acid, which can be isolated by recrystallization from EtOH (1, 2). A number of methods are based on the preparation of the ethyl (IIa) and methyl (IIb) esters of alitretinoin, which can be hydrolyzed to the corresponding carboxylic acid under alkaline conditions (3-11). In an alternative procedure, Wittig reaction of the 9-*cis*-phosphonium salts (IIIa) or (IIIb) (which can be isolated as byproducts in the production of the analogous *all-trans* derivatives) with 3-methyl-4-oxocrotonate esters (IVa/b), with concomitant ester group hydrolysis in the reaction medium, provides directly the target 9-*cis*-retinoic acid (12, 13). A different strategy consists of the condensation of the β-ionylideneacetaldehyde (V) with dimethyl β-methylglutaconate (VI) under strongly alkaline conditions to provide the diacid adduct (VII), which is mono-decarboxylated to 9,13-di-*cis*-retinoic acid (VIII) in the presence of copper acetate in hot 2,4-lutidine. Subsequent isomerization of (VIII) to the title 9-*cis*-tretinoin is accomplished by light irradiation in the presence of a trace of iodine (14). In a further synthetic route to the title compound, rearrangement of the propargylic alcohol (IX) with phenylsulfenyl chloride and triethylamine results in the conjugated sulfoxide (X) which, after desulfuration with *t*-BuLi and MeLi and desilylation with TBAF, gives 9-*cis*-retinol (XI). Finally, oxidation of alcohol (XI) utilizing MnO_2 and AgO in MeOH furnishes the target carboxylic acid (15). Scheme 1.

Alitretinoin esters (IIa) and (IIb) can be prepared by a variety of methods. Horner-Emmons reaction of either the ionylideneacetaldehyde (V) (3, 4) or its tricarbonyl iron complex (XII) (5) with diethyl 3-(ethoxycarbonyl)-2-methylprop-2-enylphosphonate (XIII), optionally followed by decomplexation using $CuCl_2$ in EtOH, provides alitretinoin ethyl ester (IIa). Alternatively, Wittig reaction of

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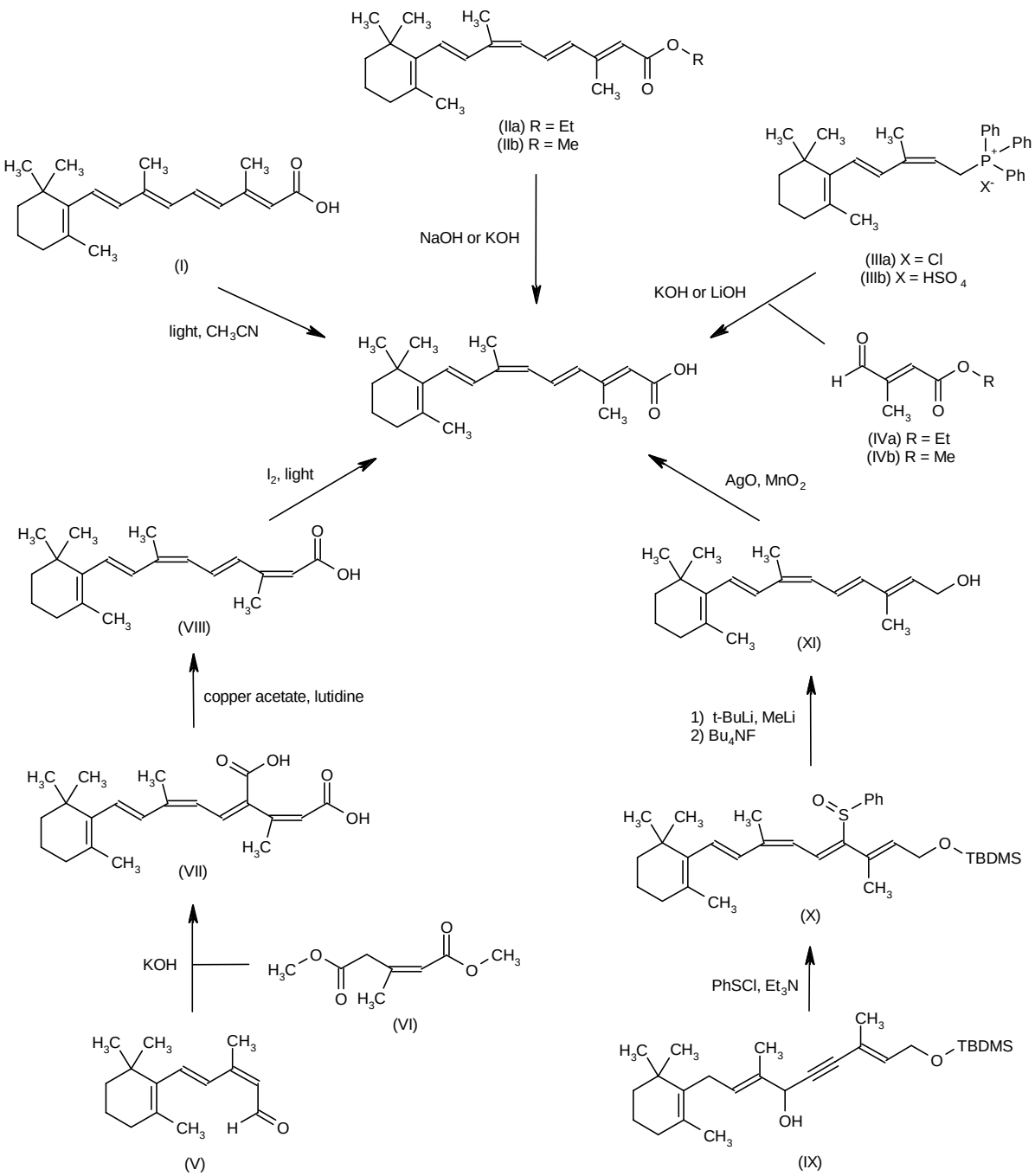
*Launched as a gel (Panretin®) in 1999 for the treatment of Kaposi's sarcoma by Ligand, which subsequently transferred rights to Eisai.

Scheme 1: Synthesis of Alitretinoin



aldehyde (V) with iodomethylenetriphenylphosphorane, followed by *in situ* elimination of HI using an excess of sodium hexamethyldisilazide, and then addition of lithium butyl(tributylstannyl)cyanocuprate to the obtained terminal acetylene, leads to the unstable vinyl stannane (XIV). Subsequent Stille coupling of crude stannane (XIV) with the vinyl triflate (XV) (derived from ethyl acetoacetate) furnishes the target 9-*cis*-retinoate (IIa) (6). In a different route, the addition of lithium butyl(tributylstannyl)-cyanocuprate (generated from Bu_3SnH, BuLi and CuCN) to (*Z*)-3-methyl-2-penten-4-yn-1-ol (XVI) and MnO_2 oxidation of the allyl alcohol function results in the stannyl dienal (XVII). Subsequent Horner-Emmons reaction of aldehyde (XVII) with phosphonate (XIII) followed by iodo-

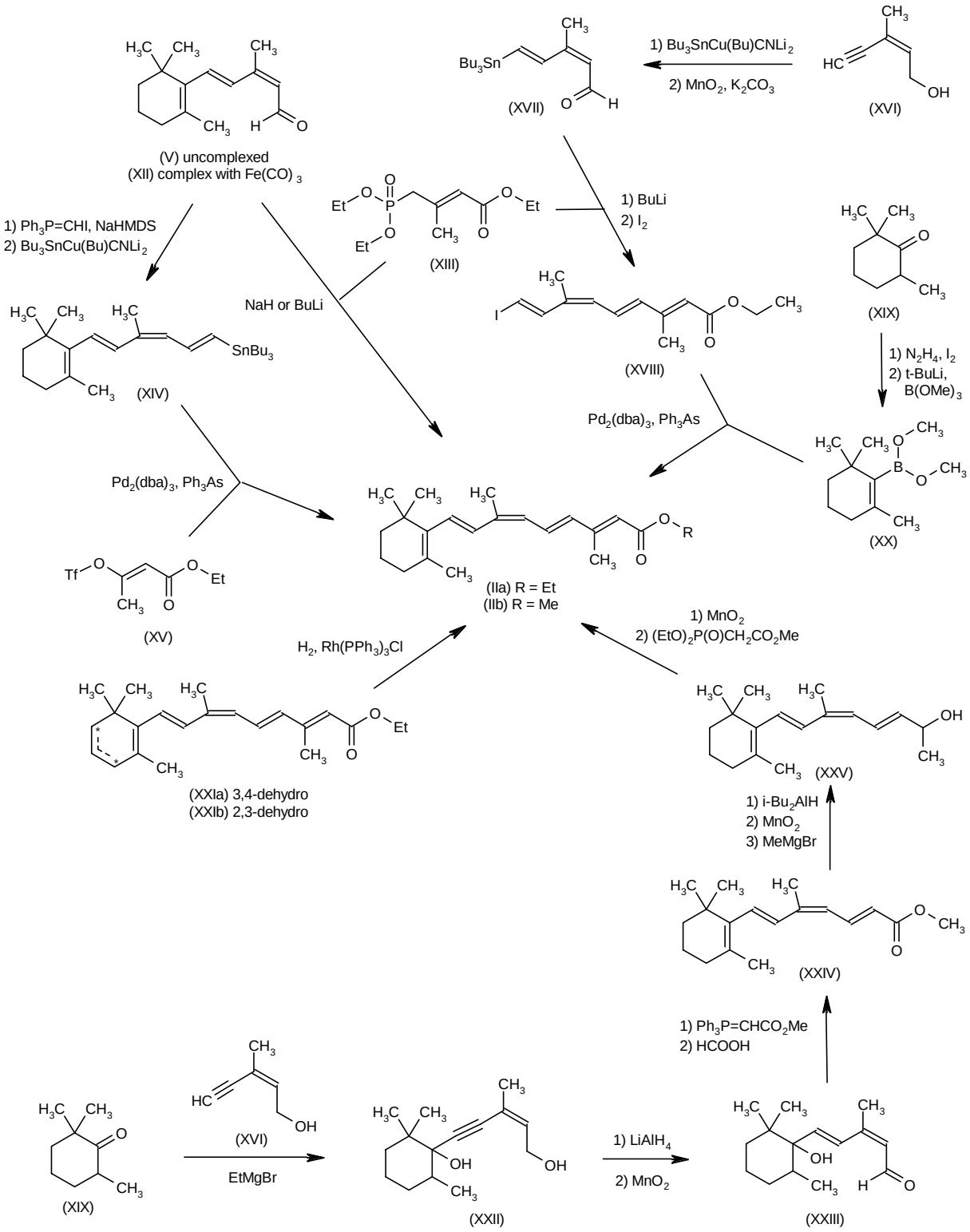
destannylation of the obtained adduct furnishes the tetraenyl iodide (XVIII). 2,2,6-Trimethylcyclohexanone (XIX) is reacted with hydrazine hydrate and Et_3N in boiling EtOH to produce the corresponding hydrazone, which is converted to vinyl iodide upon treatment with iodine and DBN. Metalation of the vinyl iodide with *t*-BuLi followed by trapping with trimethyl borate generates an unstable intermediate, assumed to be the boronic ester (XX). Then, Suzuki coupling between the *in situ*-generated boronate (XX) and freshly prepared tetraenyl iodide (XVIII) provides the target *cis*-retinoate (IIa) in satisfactory yields (7, 8). Two related synthetic strategies, useful for introducing tritium labeling onto the cyclohexenyl ring of (II), are based on the catalytic hydrogenation of the conjugated cyclohexadiene compound (XXIa) or its nonconjugated analogue (XXIb) in the presence of $Rh(PPh_3)_3Cl$ (9). Compound (IIb), along with some labeled derivatives, can be prepared by the following route. Condensation of 2,2,6-trimethylcyclohexanone (XIX) with the bromomagnesium acetylide of (*Z*)-3-methyl-2-penten-4-yn-1-ol (XVI) affords the propargylic alcohol adduct (XXII). After reduction of the triple bond of (XXII) with $LiAlH_4$, oxidation of the primary alcohol group using MnO_2 in dry CH_2Cl_2 yields the hydroxy dienal (XXIII). Wittig olefination of aldehyde (XXIII) with (methoxycarbonylmethylene)triphenylphosphorane followed by smooth dehydration of the tertiary alcohol with 80% formic acid in hexane then leads to the tetraenoate ester (XXIV). After reduction of ester (XXIV) with DIBALH and reoxidation of the obtained alcohol to aldehyde with MnO_2, the addition of methylmagnesium bromide results in the secondary alcohol (XXV). The deuterium and tritium analogues of (XXV) can be similarly obtained by using the corresponding labeled Grignard reagents. Subsequent oxidation of (XXV) with MnO_2 followed by condensation of the resulting methyl ketone with methyl diethylphosphonoacetate leads to the 9-*cis*-methylretinoate (IIb) (10, 11). Scheme 2.

The aldehyde intermediates (V) and (XII) are produced starting from β-ionone (XXVI) by several different methods. The lithium enolate of ketone (XXVI) is acylated with diethyl chlorophosphate to produce an enol phosphate intermediate, which undergoes regioselective β-elimination in the presence of LDA to furnish acetylene (XXVII). Deprotonation of (XXVII) with butyl lithium followed by treatment with phenyl cyanate gives nitrile (XXVIII), which undergoes conjugate addition of dimethyl cuprate in cold THF to afford the *cis*-trienenitrile (XXIX). Subsequent reduction of nitrile (XXIX) using DIBALH in hexane at –78 °C provides the target aldehyde (V) as the major isomer (4). Alternatively, Reformatsky reaction of β-ionone (XXVI) with the organo zinc reagent derived from ethyl bromoacetate followed by acidic dehydration produces a mixture of *cis*- and *trans*-ionylideneacetates (XXX), which, after saponification to the corresponding carboxylic acids, are separated by fractional crystallization from acetonitrile. The desired *cis*-isomer (XXXI) is then esterified by treatment with iodomethane and potassium carbonate under nonisomerizing conditions to furnish the *cis*-methyl ester (XXXIIa) (14). Reduction of ester (XXXIIa) with $LiAlH_4$ in cold THF followed by re-oxidation of the resulting alcohol with MnO_2 in CH_2Cl_2 affords aldehyde (V) (3, 14). The analogous tritium-labeled intermediate is similarly obtained utilizing $[^3H]$-$LiAlH_4$ in the reduction step (3). The tricarbonyliron complex of β-ionone (XXXIII) can be conveniently prepared by treatment of (XXVI) with dodecacarbonyltriiron(0) in boiling benzene. Condensation of (XXXIII) with the lithium enolate of ethyl acetate in cold THF gives the hydroxy ester adduct (XXXIV), which is dehydrated by means of $SOCl_2$ in pyridine to produce the (9*Z*)-conjugated ester (XXXV) as the major isomer. Reduction of ester (XXXV) with DIBALH in Et_2O at –45 °C yields the trienol derivative (XXXVI), which is converted to aldehyde (XII) without decomplexation by mild oxidation of the corresponding bromomagnesium alkoxide with azodicarbonyldipiperidine under Mukaiyama's conditions. Alternatively, decomplexation of (XXXV) with $CuCl_2$ provides the ethyl ester (XXXIIb), which is reduced to aldehyde (V) following known procedures (5). Scheme 3.

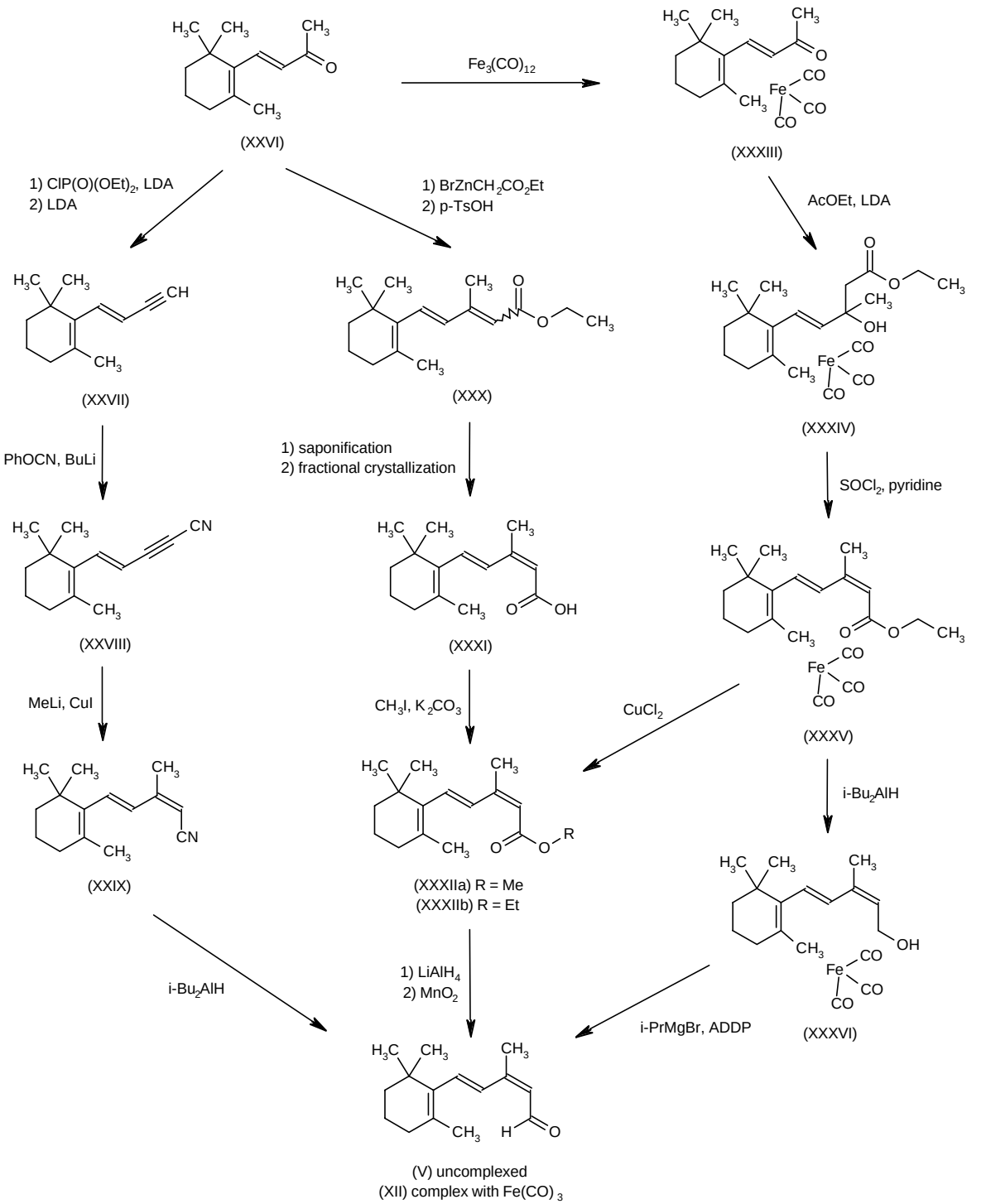
The dehydro precursors (XXIa) and (XXIb) are prepared by the following sequences. Allylic bromination of β-cyclocitral (XXXVII) with *N*-bromosuccinimide in cold CH_2Cl_2 in the presence of CaO and $NaHCO_3$ followed by elimination of HBr in boiling collidine gives α-safranal (XXXVIII). Subsequent cyclization of aldehyde (XXXVIII) with the lithium carbanion derived from ethyl 3,3-dimethylacrylate (XXXIX) in cold THF provides lactone (XLa). The analogous lactone containing an unconjugated cyclohexadiene ring (XLb) is obtained by Michael-Wittig tandem reaction of ethyl 2-isopropylideneacetoacetate (XLI) with the phosphorous ylide derived from allyltriphenylphosphonium chloride (XLII) to produce the cyclic ester (XLIII). Subsequent $LiAlH_4$ reduction of ester (XLIII) followed by Swern oxidation gives aldehyde (XLIV). After isomerization of aldehyde (XLIV) upon treatment with catalytic DBU in CH_2Cl_2 at room temperature, the isomeric cyclohexadienal (XLV) is condensed with ethyl 3,3-dimethylacrylate (XXXIX) as above to furnish lactone (XLb). Reduction of either lactone (XLa) or (XLb) with DIBALH followed by acid-catalyzed ring opening of the resulting lactols leads to the respective tetraenic aldehydes (XLVIa) and (XLVIb), which undergo Horner-Emmons olefination with diethyl 3-(ethoxycarbonyl)-2-methylprop-2-enylphosphonate (XIII) to furnish the corresponding esters (XXIa) and (XXIb) (9). Scheme 4.

The monosilylated unsaturated diol (IX) can be synthesized as follows. Darzen's condensation of β-ionone (XXVI) with ethyl chloroacetate (XLVII) in the presence of sodium methoxide affords the glycidic ester (XLVIII), which undergoes hydrolysis and decarboxylation to aldehyde (XLIX) upon treatment with methanolic NaOH (16). Protection of (*E*)-3-methyl-2-penten-4-yn-1-ol (L) with *tert*-butyldimethylsilyl chloride in the presence of imidazole and DMAP provides the corresponding silyl ether (LI) (17), which, after deprotonation with BuLi at low temperature, is condensed with aldehyde (XLIX) to provide the target propargylic alcohol (IX) (18). Scheme 5.

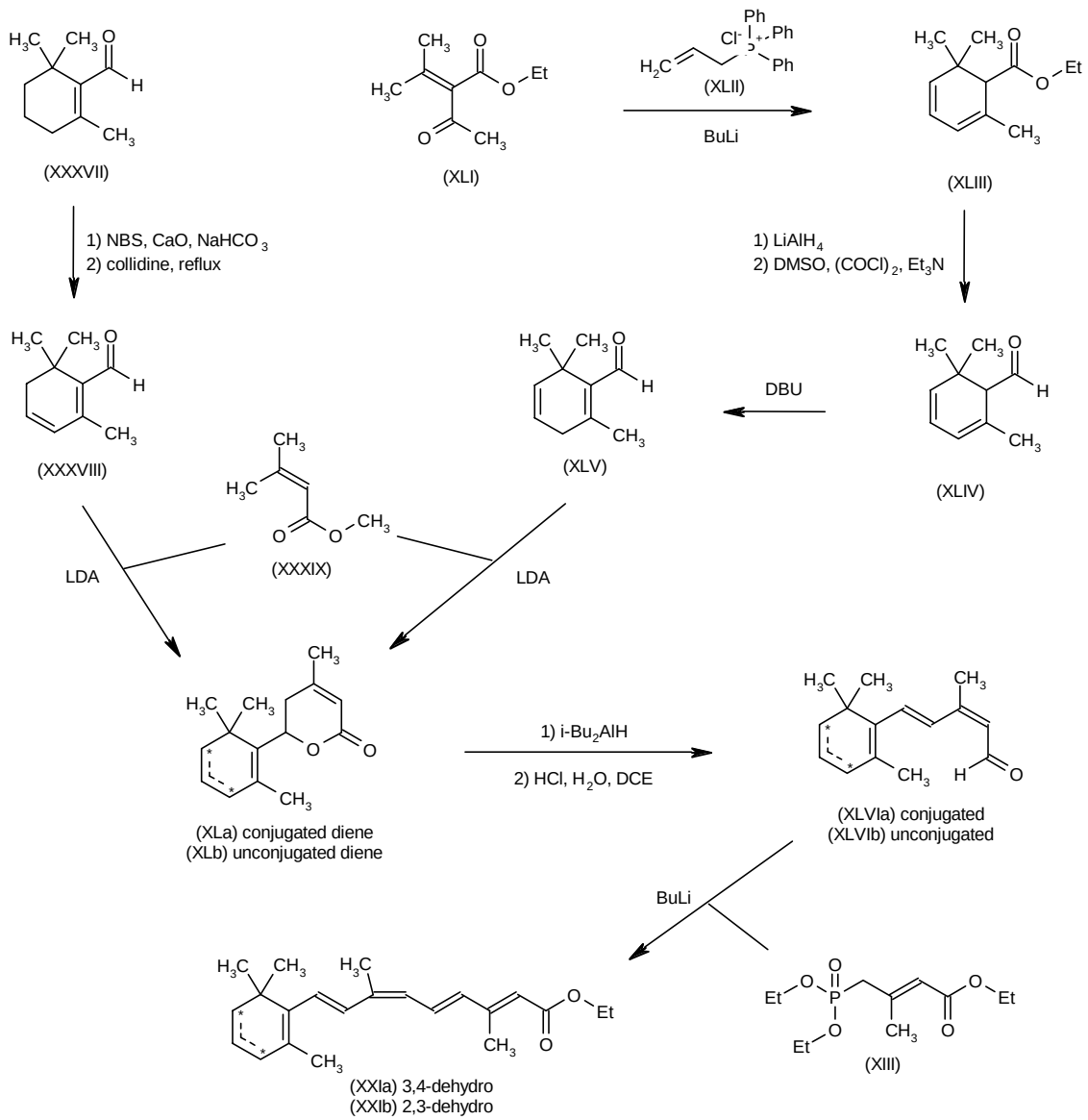
Scheme 2: Synthesis of Intermediates (IIa) and (IIb)



Scheme 3: Preparation of Intermediates (V) and (XII)



Scheme 4: Preparation of Intermediates (XXIa) and (XXIb)

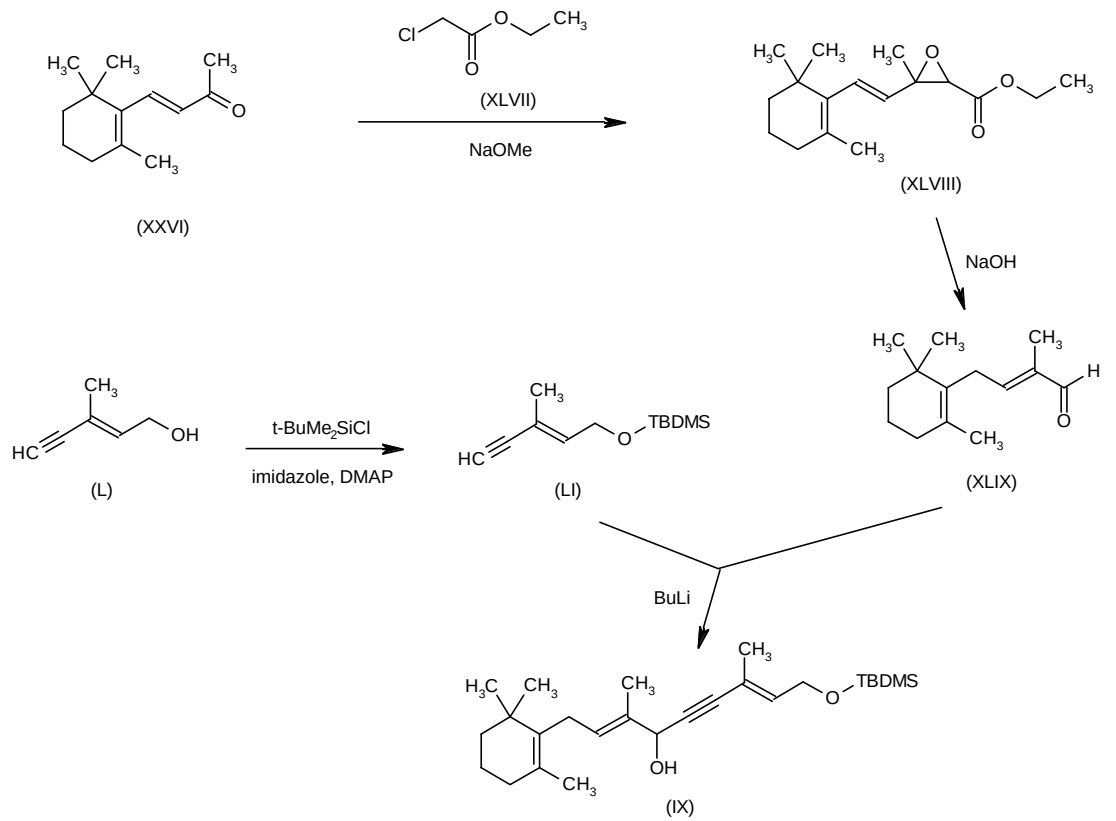


Background

Derivatives of vitamin A (retinoids) comprise a family of thousands of molecules. Retinoids bind one or more intracellular retinoic acid receptors (RARs) and/or retinoid X receptors (RXRs). Retinoids play a crucial role in fetal development, bone assembly, cell proliferation, cell differentiation, apoptosis, hematopoiesis, immune function and vision. Alitretinoin (9-*cis*-retinoic acid) is an endogenous retinoid that activates all RAR and RXR receptors and is currently approved for use as a topical gel for Kaposi's sarcoma (19, 20). It has also successfully completed trials as an oral medication for the treatment of chronic (refractory) hand dermatitis.

Alitretinoin was developed based on the chemical structure of *all-trans*-retinoic acid (ATRA, or tretinoin). Tretinoin is an effective treatment for acute promyelocytic leukemia (APL) and hairy cell leukemia (HCL), and is able to induce complete hematological and cytogenetic remissions of both diseases. The limitations of tretinoin include: 1) reduced plasma levels of retinoic acid during continuous therapy, likely secondary to increased metabolism; 2) relapse of APL after a comparatively short remission due to rapid development of retinoid resistance despite continuing therapy; and 3) adverse (dose-related) reactions such as leukocytosis, dyspnea and, in a minority of patients, a syndrome characterized by fever, respiratory distress, weight gain, edema and pleural or pericardial effusions (21).

Scheme 5: Preparation of Intermediate (IX)



Preclinical Pharmacology

Alitretinoin binds to and activates all known intracellular retinoid receptor subtypes (RARα, RARβ, RARγ, RXRα, RXRβ and RXRγ). Once activated, these receptors function as transcription factors that regulate the expression of genes involved in the differentiation and proliferation of both normal and neoplastic cells. By comparison, tretinoin binds primarily to RARs, with very low affinity for RXRs (20). Isotretinoin (13-*cis*-retinoic acid) indirectly activates RARs and has little or no effect on RXRs (22).

Alitretinoin binds with higher affinity to RARs than RXRs, with dissociation constants (K_d) of 0.31 ± 0.07, 0.20 ± 0.09 and 0.78 ± 0.14 nmol/l for RARα, RARβ and RARγ, respectively, in cell extracts containing recombinantly expressed receptor proteins. K_d values for the RXR subfamily are 1.62 ± 0.34, 2.36 ± 0.76 and 2.29 ± 0.84 nmol/l, respectively, for RXRα, RXRβ and RXRγ (23).

Pharmacokinetics and Metabolism

The pharmacokinetics of alitretinoin were determined in rhesus monkeys following i.v. bolus administration of 50 or 100 mg/m^2 of the drug. The plasma drug profile exhibited first-order elimination, with a mean half-life of 31 min and a mean clearance of 97 ml/min/m^2. Research suggests that repeated administration of alitretinoin at doses between 0.01 and 100 mg/m^2 will not result in declining plasma concentrations (24).

After topical application of alitretinoin gel, 9-*cis*-retinoic acid metabolites were not detectable in plasma. *In vitro* experiments suggested that alitretinoin is metabolized to 4-hydroxy-9-*cis*-retinoic acid and 4-oxo-9-*cis*-retinoic acid by cytochrome P-450 (CYP) 2C9, 3A4, 1A1 and 1A2 enzymes. *In vivo*, 4-oxo-9-*cis*-retinoic acid is the major circulating metabolite following oral administration of alitretinoin (25).

Clinical Studies

There is a growing body of evidence suggesting that, in addition to being an effective treatment for Kaposi's sarcoma, oral alitretinoin may be employed in the treatment of chronic (refractory) hand dermatitis (CHD). Hand dermatitis has a wide range of manifestations, including contact (*e.g.*, allergic [which can be acute, subacute or chronic] and irritant), hyperkeratotic (*e.g.*, psoriasiform, plaque and tylotic), frictional (*e.g.*, lichen simplex chronicus, fissuring, callus-like or involving calluses), nummular (which is very rare on the hands), atopic, pompholyx

(*e.g.*, dyshydrotic dermatitis) and vesicular hand dermatitis. All types of CHD are usually chronic but can also be acute.

Bollag reported the results from a study for the treatment of hand dermatitis in 1999. Thirty-eight patients with refractory chronic hand eczema were treated in an exploratory open-label study with oral alitretinoin. Twenty-one (55%) showed a very good response, 13 (34%) a good response, 2 (5.5%) a moderate response and 2 (5.5%) no response. Only mild side effects were reported and it was concluded that low doses of alitretinoin provide a useful therapeutic option for patients with chronic hand eczema (26).

Larger studies have also shown that alitretinoin improves the symptoms of refractory CHD. A daily regimen of oral alitretinoin induced clinical responses in up to 53% of patients with moderate to severe CHD refractory to standard topical therapy, and it reduced the signs and symptoms of the disease by up to 70%, according to the results of a multicenter, randomized, double-blind, placebo-controlled, prospective study (27). To evaluate the safety and efficacy of alitretinoin, the investigators recruited 319 patients with CHD refractory to standard topical therapy. Patients were randomized to receive 10, 20 or 40 mg/day of alitretinoin or placebo for 12 weeks. Assessments were performed at the end of the trial and at a 3-month follow-up. To determine the efficacy of alitretinoin, Ruzicka utilized the Physician's Global Assessment of overall CHD severity, the Patient's Global Assessment of improvement and the total lesion symptom score (TLSS). Patients with Physician's Global Assessment ratings of clear (no residual visible dermatitis) or almost clear (minimal erythema and/or scaling) were considered responders. The investigators determined that alitretinoin produced a significant and dose-dependent effect on Physician's Global Assessment scores ($p < 0.001$) compared to placebo. Response rates of 39%, 41% and 53%, respectively, were obtained on doses of 10, 20 and 40 mg (placebo: 27%). The investigators attributed the response rate observed in the placebo group to spontaneous variability that may be more common in patients with less severe disease. The Patient's Global Assessment scores demonstrated a similar pattern, with response rates of 29%, 34% and 43%, respectively, on doses of 10, 20 and 40 mg alitretinoin, which were clinically significant compared to placebo ($p = 0.01$, $p = 0.002$ and $p < 0.001$, respectively). Clinical improvement was seen for all types of CHD (hyperkeratotic and fingertip eczema, pompholyx), even in those cases which were previously unresponsive to all therapies. A dose-dependent ($p < 0.001$) improvement was observed in TLSS scores from baseline for all doses of alitretinoin compared to placebo ($p < 0.001$). TLSS scores improved compared to baseline by 59% in the 10 mg/day group, 52% in the 20 mg/day group and 70.5% in the 40 mg/day group. Alitretinoin was generally well tolerated, with similar adverse event rates among the placebo and 10- and 20-mg dose groups. However, adverse events were observed on the 40 mg/day dose, including headache, flushing, elevation in serum lipid levels, slightly decreased hemoglobin level and decreased free thyroxin level. Of the initial responding patients, 26% required prescription therapy for their CHD during the 3-month follow-up period and thus were deemed to have relapsed. Relapse rates were similar in all dose groups.

In May 2007, the results of an international, prospective, randomized, double-blind, placebo-controlled, parallel-group phase III study —the Benefit of Alitretinoin in Chronic Hand Dermatitis (BACH) study— were presented at the 16th European Academy of Dermatology and Venereology Congress (EADV) (28). The results showed that oral alitretinoin was effective for the treatment of CHD. This study was designed to determine whether doses of 10 and 30 mg of alitretinoin were superior to placebo following 12 and 24 weeks of treatment. Patients in the study had severe chronic hand eczema as defined by the Physician's Global Assessment that was refractory to potent topical steroids. Patients included those with allergic contact dermatitis for at least 6 months, but the mean disease duration was approximately 9 years. Patients in the study had treatment failure while on the most potent steroids. Judging by the lower doses administered in this study, it appears that the BACH investigators sought to avoid the side effects observed in the 40-mg group in Ruzicka's study. Following eligibility prescreening, the BACH investigators randomized 1,032 patients to placebo (n=205), alitretinoin 10 mg (n=418) or 30 mg (n=409) given once daily for 12 or 24 weeks, depending on the treatment response. A standard moisturizer was to be applied by patients several times daily. Patients' mean age was 47.9 years in the placebo group (59.0% male), 47.3 years in the 10-mg group (56.9% male) and 48.5 years in the 30-mg group (54.5% male). The investigators balanced the baseline clinical characteristics across the three treatment groups, including duration of disease and disease phenotypes: hyperkeratotic (82.9%, 86.6% and 85.3%, respectively), pompholyx (26.8%, 26.6% and 27.1%, respectively), fingertip (49.3%, 43.1% and 47.9%, respectively) and other (14.1%, 14.5% and 13.4%, respectively). Women of childbearing age used birth control. The investigators determined the primary endpoint of Physician's Global Assessment response rates at the end of therapy as the percentage of responders clear or almost clear of disease, with increasing significant improvements seen for placebo (17%; $p < 0.001$), alitretinoin 10 mg (28%; $p = 0.004$) and alitretinoin 30 mg (48%; $p < 0.001$). This dose-dependent efficacy was confirmed for the secondary endpoints: Patient's Global Assessment (patients with clearing: 15%, 24% and 40%, respectively) and median percentage reductions in modified TLSS (mTLSS; 39%, 56% and 75%, respectively) and extent of disease (33%, 50% and 75%, respectively). Treatment-related adverse events were seen in 34.5%, 37.1% and 49.5% of patients, respectively (headache: 6.4%, 10.8% and 19.8%, respectively). Only 1% of patients in each treatment group reported severe adverse events. A single death was recorded in the low-dose alitretinoin group.

The researchers noted several anomalous laboratory values in the placebo, alitretinoin 10 and 30 mg treatment groups, specifically high cholesterol (3.2%, 3.1% and 14.2%, respectively), elevated triglycerides (2.4%, 3.5% and 7.7%, respectively) and low thyroid-stimulating hormone (2%, 5.3% and 6.9%, respectively).

A marketing authorization application (MAA) seeking approval for the use of the drug in the treatment of severe refractory chronic hand eczema is presently under review by the European and Swiss health authorities (29).

Source

Basilea Pharmaceutica AG (CH).

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