U.S. FOOD & DRUG ADMINISTRATION

A

ND 211000 A

ANDA TENTATIVE APPROVAL

mneal Pharmaceuticals of New York, LLC
U.S. gent for mneal EU, Limited
ttention: Janie M. Gwinn
Vice President, Regulatory ffairs

Dear Janie M. Gwinn:

This letter is in reference to your abbreviated new drug application (ND) received for review on October 18, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic ct (FD&C ct) for Macitentan Tablets, 10 mg.

Reference is also made to the complete response letter issued by this office on ugust 16, 2018, and to any amendments thereafter.

We have completed the review of this ND and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C ct. We have determined your Macitentan Tablets, 10 mg to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Opsumit Tablets, 10 mg, of ctelion Pharmaceuticals US, Inc. (ctelion) ND - 204410.

However, we are unable to grant final approval to your ND at this time because of the exclusivity issue noted below. Therefore, the ND is **tentatively approved**. This determination is based upon information available to the gency at this time (e.g., information in your ND and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug (RLD) upon which you have based your ND , ctelion's Opsumit Tablets, 10 mg, is subject to periods of patent protection. The following patents and expiration dates (with pediatric exclusivity added) are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence* A *Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
7,094,781 (the '781 patent)	June 5, 2026 A
8,268,847 (the '847 patent)	October 18, 2029

8,367,685 (th '685 p t nt)	April 4, 2029
9,265,762 (th '762 p t nt)	Nov mb r 29, 2027
10,946,015 (th '015 p t nt)	M arch 11, 2027

Your ANDA cont ins p r r ph IV c rtific tions to th '847, '685, '762, and '015 p t nts und r s ction 505(j)(2)(A)(vii)(IV) of th FD&C Act st tin th t th p t nts r inv lid, un nforc bl , or will not b infrin d by your m anuf ctur , us , or s l of M acit nt n T bl ts, 10 m g, und r this ANDA. You h v notifi d th A ncy th t Amn l EU, Limit d (Amn l) compli d with th r quir m ents of s ction 505(j)(2)(B) of th FD&C Act, nd th t no ction for infrin m ent of the '847, '685, '762 patents w s brou ht inst Amn l within th st tutory 45-d y p riod.

The RLD upon which you have based your ANDA, Actelion's Opsumit Tablets, 10 mg, is subj ct to p riods of xclusivity. As not d bov , th p di tric xclusivity p riod ssoci t d with th '781 p t nt is sch dul d to xpir on Jun 5, 2026.[2] Th r for , fin l pprov l c nnot b r nt d until xpir tion of th p di tric xclusivity p riod ssoci t d with th '781 p t nt. S s ction 505A(b)(1)(B)(i) of th FD&C Act. [21]

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

S ction 505-1 of th FD&C Act uthoriz s FDA to r quir th submission of risk v lu tion nd miti tion str t y (REMS), if FDA d t rmin s th t such str t y is n c ss ry to nsur th t th b n fits of th dru outw i h th risks [s ction 505-1( ) of th FD&C Act]. In ccord nc with s ction 505-1(i) of th FD&C Act, dru th t is th subj ct of n ANDA und r s ction 505(j) is subj ct to c rt in l m ents of th REMS r quir d for th pplic bl list d dru .

In our l tt r d t d D c mb r 1, 2017, w notifi d you th t REMS is r quir d for m acit nt n-cont inin products to nsur th t th b n fits of th dru outw i h th risk e of mbryo-f t l toxicity. We indic t d th t your REMS must includ l m ents to ssur s f us nd n impl m ent tion syst m.

We h v d t rmin d th t, t this tim e, REMS is no lon r n c ss ry for m acit nt n-cont inin products, to nsur th t its b n fits outw i h its risks. We will notify you if w b com e w r of n w s f ty inform ation nd m ak d t rmin tion th t REMS is n c ss ry.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL e

Und r pplic bl st tut s, r ul tions, nd uid nc s, if your ANDA r c iv s fin l pprov l, it m ay b subj ct to c rt in r quir m ents nd r comm nd tions post pprov l, includin r quir m ents r rdin ch n s to pprov d ANDAs, postm ark tin r portin , promotion l m at ri ls, nd nnu l f cility f s, mon oth rs. For inform ation e

on post- pprov l r quir m nts nd r commend tions for ANDAs nd list of r sourc s for ANDA hold rs, w r f r you to https://www.fd . ov/dru s/ bbr vi t d-n w-dru - pplic tion- nd /r quir m nts- nd-r sourc s- pprov d- nd s.

RESUBMISSION

To request final approval, please submit an amendment titled "FINAL APPROVAL REQUESTED" with enough time to permit FDA review prior to the date you believe that your ANDA will b li ibl for fin l pprov l. A r qu st for fin l pprov l th t cont ins no n w d t , inform ation, or oth r ch n s to th ANDA n r lly r quir s p riod of months for A ncy r vi w. Accordin ly, such r qu st for fin l pprov l should b submitt d no l t r th n months prior to th d t on which you s k pprov l. A r qu st for fin l pprov l th t cont ins subst ntiv ch n s to this ANDA or ch n s in the status of the manufacturing and testing facilities' compliance with cGMPs will be cl ssifi d nd r vi w d ccordin to OGD policy in ff ct t th tim e of r c ipt. Applic nts should r vi w v il bl ncy uid nc for industry r l t d to m endm nts und r th n ric dru us r f pro r m to d t rmin th dur tion of A ncy r vi w v n d d to r vi w th ch n s submitt d. As p rt of this consid r tion, pplic nts should monitor ny ch n s to th RLD th t occur ft r t nt tiv pprov l, includin ch n s in l b lin , p t nt or xclusivity inform ation, or m ark tin st tus. Th submission of multipl m endm nts prior to fin l pprov l m ay lso r sult in d l y in th issu nc of th fin l pprov l l tt r.

Th m endm nt r qu stin fin l pprov l should provid th l l/r ul tory b sis for your r qu st for fin l pprov l nd should includ copy of court d cision, s ttl m nt or lic nsin r m nt, or oth r inform ation d scrib d in 21 CFR 14.107, s ppropri t . It should lso id ntify ch n s, if ny, in th conditions und r which th ANDA w s t nt tiv ly pprov d, . ., upd t d inform ation such s fin l-print d l b lin , ch mistry, m anuf cturin , nd controls d t s ppropri t . This m endm nt should b submitt d v n if non of th s ch n s w r m ad , nd it should b d si n t d clearly in your cover letter as a "FINAL APPROVAL REQUESTED."

In ddition to th m endm nt r qu st d bov , th A ncy m ay r qu st, t ny tim e prior to th d t of fin l pprov l, th t you submit n ddition l m endm nt cont inin v inform ation s sp cifi d by th A ncy. F ilur to submit ith r or, if r qu st d, both typ s of m endm nts d scrib d bov m ay r sult in d l y in th issu nc of th fin l pprov l l tt r.

This dru product m ay not b m ark t d without fin l A ncy pprov l und r s ction 505(j) of th FD&C Act. Th introduction or d liv ry for introduction into int rst t comm rc of this dru product b for th fin l pprov l d t is prohibit d und r s ction v 01 of th FD&C Act. Also, until th A ncy issu s th fin l pprov l l tt r, this dru product will not b d m ed pprov d for m ark tin und r s ction 505(j) of th FD&C Act, nd will not b list d in th Or n Book. v

For furth r inform ation on th st tus of this ANDA or upon submittin n m endm ent to th ANDA, pl s cont ct Kimb rly McCullou h, R ul tory Proj ct M an r, t (2 0) 02 - 9021.

Sinc r ly yours,

{See appended electronic signature page}

For K ndr S. St w rt, R.Ph., Ph rm.D.
CAPT, Unit d St t s Public H lth S rvic
Dir ctor
Offic of R ul tory Op r tions
Offic of G en ric Dru s
C nt r for Dru Ev lu tion nd R s rch v

---

[1] Althou h your ANDA pr viously cont in d p r r ph IV c rtific tion to th '781 p t nt, upon xpir tion of th t p t nt on D c mb r 5, 2025, your c rtific tion to th '781 p t nt is d m ed to b p r r ph II c rtific tion.

[2] We not th t this ANDA curr ntly is li ibl for pprov l th d y ft r xpir tion of th p di tric xclusivity p riod. S S ction 505A(b)(1)(B) of th FD&C Act. If this d y f lls on S turd y, Sund y, v or F d r l holid y, it will b li ibl for pprov l th n xt busin ss d y.

Paul c
Levi e c

i i a l si ed b Paul Levi e
a e: 2/25/2026 06:44:47AM
GUI : 56323dd 003554a87fad6698 2baa467 c