CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203312Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: January 18, 2013

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 203-312 (Rytary™, carbidopa-levodopa extended release capsules, IPX066)

NDA 203-312 for Rytary, an extended release formulation of carbidopa-levodopa (CD-LD) for treatment of Parkinson's disease, was submitted as a 505(b)(2) application on December 21, 2011. During the NDA review, the relatively high levels of four excipients in the to-be-marketed drug product were identified as potential safety issues. Sufficient data were provided to support the levels of all but one excipient, [redacted] (b) (4) (*cf. Memorandum, NDA 203-312, Lois M. Freed, Ph.D., 12/6/2012*). A teleconference was held with the sponsor (9/21/2012) to convey the potential deficiency issues. In response, the sponsor submitted additional information on September 28, 2012 (received October 2, 2012), which was determined to constitute a major amendment (*Agency Review Extension-Major Amendment letter, 10/4/2012; teleconference with sponsor, 10/11/2012*). As a result, the goal date was extended by three months, to January 21, 2013.

The following information was provided in the October 2, 2012 amendment:

- [redacted] (b) (4) - Impax Laboratories, Inc.
- Independent Report - [redacted] (b) (4)
- References

In the [redacted] (b) (4) the sponsor provided a summary and discussion of the available safety data on [redacted] (b) (4) and related [redacted] (b) (4) (e.g., [redacted] (b) (4)). Based on "a more comprehensive review" of the toxicity studies of [redacted] (b) (4) conducted by the manufacturer [redacted] (b) (4) the sponsor concluded that dose-related histopathological findings in thyroid gland were detected in mouse, rat, and rabbit but that the clearest evidence was observed in rat; the dose of 100 mg/kg/day was the NOAEL in all three species. (However, the duration of dosing was substantially longer in rat compared to the other species, i.e., 6 months vs 6 weeks.) The sponsor also noted that

the mechanism underlying the thyroid findings "remains unclear in light of…studies which clearly indicate non-absorption of the copolymer." (No absorption study was conducted for [redacted].) The sponsor was asked to submit any available information to address the possibility that the thyroid finding were due to local (GI) effects; no information was provided. The sponsor did discuss, to some extent, species differences in sensitivity to xenobiotic-induced thyroid effects, noting that "…there are several species differences in thyroid physiology that account for a poor capacity of rodent and rabbit findings to predict thyroid toxicity in humans." Most of the information was on the well-known greater sensitivity of rat to thyroid toxicity caused, for example, by cytochrome P450 enzyme inducers [redacted]. The sponsor cited one publication [redacted] which would be consistent with greater sensitivity in that species. The sponsor also stated that "…lagomorph thyroid glands are more active and operate at a higher level with respect to thyroid hormone turnover as compared to the human thyroid…" but cited only a personal communication in support. No supportive information was provided on the mouse.

The Independent Report prepared by [redacted] provided a discussion of published literature on the [redacted] thyroid toxicity, primarily in rat, focusing on thyroid carcinogenicity. [redacted] noted that thyroid of human and monkey are less sensitive than rodent (again, primarily rat) to xenobiotic-induced effects on the pituitary-thyroid axis; thyroxine-binding protein is present in plasma of human and monkey but not rat or mouse. No information was provided related to the sensitivity of rabbit compared to human.

Comments: the information provided by the sponsor confirms the findings identified in the original NDA submission. That is, thyroid gland was a target organ for toxicity in multiple species (mouse, rat, and rabbit) administered [redacted] orally for 6 weeks or 6 months. The sponsor noted that the mechanism by which thyroid gland toxicity was induced is unknown but believes that the thyroid findings "may not be directly applicable to humans owing to significant species differences in the regulation of thyroid function."

It is acknowledged that the rat thyroid gland may be substantially more sensitive than humans to xenobiotic-induced effects on thyroid gland. This may also be true of mouse and rabbit, although the sponsor provided fewer data for these species, particularly the rabbit. However, based on the data provided, it is difficult to completely dismiss concerns regarding the findings with [redacted] due, in part, to the lack of information on mechanism of action. As noted by [redacted] in relationship to xenobiotic-induced thyroid hyperplasia, "…evaluation of risk of such endocrine hyperplasia for humans requires careful characterization of the related hormonal and enzymatic changes in animals and design of clinical studies that permit assessment of similar endpoints in humans." According to the study reports for the 6-week studies in mouse and rabbit, it could not even be determined "…whether these [histopathology] changes might represent hypo- or hyperfunction of the thyroids."

Although humans may be less sensitivity than certain animal species, there certainly are cases of xenobiotic-induced adverse effects on thyroid function in humans (b) (4) . According to the clinical team, the clinical trials of Rytary were not designed to detect changes in thyroid function; in addition, it would be very difficult to detect adverse effects on thyroid gland in humans through post-marketing surveillance.

As or more important than the human relevance of the thyroid findings in multiple animal species is the fact that these findings are evidence of systemic toxicity; systemic toxicity is unexpected for an excipient with such a high molecular weight. If, in fact, (b) (4) -related material, when administered orally, exert systemic effects, then the available nonclinical data are not adequate to support chronic administration in humans, particularly at the levels present in Rytary. Only a single standard chronic toxicity study of Rytary was conducted (6-month study in rat); there are no chronic toxicity studies in non-rodent and no assessment of reproductive and developmental toxicity or of carcinogenic potential. Arguing against a systemic effect is, as previously noted, the high molecular weight of (b) (4) . Also, although the monomers which comprise (b) (4) (b) (4)) have been reported to produce toxicity in mouse, rat, dog, and human (discussed in the sponsor's (b) (4)), the specification limits for these monomers in Rytary are acceptable.

The same (b) (4) batch was used in the 6-month toxicity studies in rat and the 6-week toxicity studies in mouse and rabbit, which were initiated in 1984-1989. Considering the age of the studies, the likelihood of limited oral bioavailability of (b) (4) (although not tested), and the lack of an understanding of how local (GI) effects could lead to the thyroid findings observed, it seems possible that the thyroid findings in these studies may have been due to some unidentified impurity in the batch used in all four studies. Therefore, before requiring additional nonclinical studies of the excipient, it seems reasonable to have the sponsor assess the oral bioavailability of (b) (4) and confirm the findings of the previous studies with a batch of (b) (4) that is representative of the quality of the currently manufactured excipient.

Recommendation

It is recommended that the sponsor be required to conduct the following nonclinical studies of (b) (4) :

- Oral absorption study using radiolabeled excipient.
- Six-month oral toxicology study in rat.

If the NDA is ready for approval prior to completion of these studies, there is no objection to them being completed post-approval, as Post-Marketing Requirements.

Note: the nonclinical PMRs were conveyed to the sponsor (teleconference, 12/4/2012; email communication, 12/6/2012). The sponsor agreed to conduct the studies and provided dates for completion in a December 7, 2012 submission to the NDA (S-0031).

It has since been determined that a Complete Response (CR) action will be taken; therefore, labeling recommendations will not be documented and the nonclinical PMRs will not be imposed at this time.

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/s/

LOIS M FREED
01/18/2013

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: December 5, 2012

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 203-312 (IPX066, carbidopa-levodopa extended release capsules)

NDA 203-312 for IPX066, an extended release formulation of carbidopa-levodopa (CD-LD) for treatment of Parkinson's disease, was submitted as a 505(b)(2) application on December 21, 2011; the reference listed drugs (RLD) are Sinemet (NDA 17-555), Lodosyn (NDA 17-830), Sinemet CR (NDA 19-856), and Stalevo (NDA 21-485). As conveyed to the sponsor in meetings held under IND 102887, no new nonclinical studies would be needed unless issues arose (e.g., changes in the impurity profile) that would require additional nonclinical data (*cf. Memorandum of Meeting Minutes, 10/14/2008; Memorandum of Meeting Minutes, 9/28/2011*). The nonclinical section of the NDA provided only copies of published literature and a safety report on excipients, (b) (4) , prepared for the sponsor by (b) (4) . This information was reviewed by Dr. LuAnn McKinney (*Pharmacology/Toxicology NDA Review and Evaluation, NDA 203-312, LuAnn McKinney, D.V.M., 9/25/2012*). Based on her review, Dr. McKinney has concluded that there are no safety concerns and recommends approval of the NDA, assuming a maximum human daily dose (MHDD) of ten 61.25-245 mg LD-CD capsules. Currently, draft labeling provides for up to fifteen 61.25-245 mg LD-CD capsules.

Excipients

The drug product contains numerous inactive ingredients, none of which is a novel excipient. However, according to the sponsor, four of these ((b) (4) , triethyl citrate, and (b) (4) tartaric acid) are present in IPX066 at per-capsule amounts that do not exceed the "maximum potency" (i.e., "the maximum amount of inactive ingredient for each route/dosage form containing that ingredient") amounts listed in the Inactive Ingredients Database (IID) but that would exceed these amounts at the maximum daily dose specified in sponsor's proposed labeling.

Triethyl citrate and (b) (4) tartaric acid

The maximum potency, as listed in the IID, is (b) (4) and (b) (4) mg for triethyl citrate and (b) (4) tartaric acid, respectively. For IPX066, the per-capsule amounts of these excipients are provided in the table below.

EXCIPIENT	IPX066 ER			
	23.75-95 mg	36.25-145 mg	48.75-195 mg	61.25-245 mg
triethyl citrate	(b) (4)			
(b) (4) tartaric acid				

Triethyl citrate and (b) (4) tartaric acid are both endogenous compounds and both are affirmed to be GRAS by the FDA. According to the Select Committee on GRAS Substances (SCOGS), triethyl citrate and (b) (4) tartaric acid are added to foods at amounts resulting in 500 mg/day (similar to that in 2 oz of orange juice) and 0.2 mg/kg/day, respectively. The total daily dose of triethyl citrate at the MHDD of IPX066 (according to the sponsor) would be (b) (4) well within GRAS amounts. While the total daily dose of (b) (4) tartaric acid (b) (4) exceeds GRAS amounts, according to the SCOGS opinion:

> "Daily ingestion of 2.3g per kg of body weight per day for 150 days produced no ill effects in rabbits. No toxicity was found in rats ingesting up to (b) (4) g per kg of body weight of tartaric acid in the diet daily for 2 years."

The sponsor cited a number of sources in support of the total daily dose of (b) (4) tartaric acid from IPX066: FDA MRTD Database, 21CFR150.151 and 21CFR73.170, and Joint FAO/WHO Expert Committee on Food Additives (JECFA). The only daily limit specified by any of these sources was 30 mg/kg/day. This limit was stated by FDA's MRTD Database and "established [by JECFA as] an unconditional ADI…from all sources…" The sponsor referenced the CFR citations to support use of (b) (4) tartaric acid in "a variety of foods and over-the counter drugs…" However, these citations only described the presence of (b) (4) tartaric in grape seed extract or as an ingredient in artificially sweetened fruit jelly; neither addressed the use of (b) (4) tartaric acid in over-the counter drug products. The summary JECFA evaluation, apparently conducted in 1977 (the sponsor specifies November 21, 2002 as the date), identifies the ADI for (b) (4) tartaric acid as 0-30 mg/kg bw. The 1977 JECFA report (#617) summarized the available data on various forms of tartaric (b) (4) these data did not suggest notable general or reproductive/developmental toxicity. The total daily dose of (b) (4) tartaric acid at the MRHD of IPX066 is slightly higher than the ADI determined by JECFA. Although, as Dr. McKinney notes, the JECFA evaluation does not reflect review by the FDA, the JECFA conclusion is consistent with FDA's discussion of toxicity studies of (b) (4) tartaric acid.

(b) (4)

Dr. McKinney's review focused primarily on the levels of (b) (4) in the drug product (provided in the table below; units of mg/capsule).

EXCIPIENT	IPX066 ER			
	23.75-95 mg	36.25-145 mg	48.75-195 mg	61.25-245 mg
(b) (4)				

(b) (4) have an average molecular weight of (b) (4) and are copolymers comprised of molar ratios (b) (4) of (b) (4) (structures provided below, from the sponsor).

(b) (4)

According to the sponsor, the MHDD of IPX066 is to be (b) (4) capsules of the 61.25-245 mg (CD-LD) strength capsule, or (b) (4) mg/day CD-LD. This MHDD would result in total daily doses of (b) (4) (b) (4) mg, respectively. According to the IID, (b) (4) are in approved drug products at unit amounts up to (b) (4), respectively. On a (b) (4) basis, the amount of each excipient in IPX066 is less or similar to the maximum amount in approved drug products. However, based on the sponsor's proposed MHDD of IPX066, the sponsor indicates that the daily intake of both excipients would exceed those resulting from therapeutic use of approved drug products containing one or more of these excipients.

To support the safety of the proposed daily doses of (b) (4), the sponsor provided an LoA from (b) (4) to DMF (b) (4) and a summary evaluation of the safety data for these excipients prepared by (b) (4). Dr. McKinney reviewed the summary evaluation and two 6-month oral toxicity studies provided in the DMF (b) (4) (b) (4) In addition, nonclinical data contained in DMF (b) (4) have been reviewed by several reviewers (including Kwadwo Awuah, Ph.D., OGIEP; Sushanta K. Chakader, Ph.D., DGIEP; Dinesh Gautam, Ph.D, OGIEP; Terry S. Peters, D.V.M., DAIDP) in support of other drug applications (for each, an LoA was provided by the DMF holder). Based on these reviews and with reference to the study reports for the two 6-month toxicity studies of (b) (4) in Wistar rat, the findings are summarized as follows:

[redacted]

Absorption: absorption was reported to be minimal following an acute oral dose of 80 mg/kg radiolabeled [redacted] to fasted Wistar rats [redacted] final report dated [redacted]).

Toxicity: minimal acute oral (gavage) toxicity was reported, with LD_{50}'s of >10,000 mg/kg, >3000 mg/kg, >15,900 mg/kg, and >10,000 mg/kg in dd mice, Wistar rat, Sprague-Dawley rat, and "cross-bred" dogs, respectively, in studies conducted in [redacted]

In a 30-day oral (gavage) toxicity study in Sprague-Dawley rat (0, 500, 2000 mg/kg), no toxicity was reported up to a maximum feasible dose ([redacted], final report dated [redacted]; stated to be GLP compliant by [redacted]).

In a 90-day oral (gavage) toxicity study in rat (strain not specified), the combination of [redacted] at doses of 0, 15.5, and 77.5 mg/kg/day resulted in no evidence of toxicity (only liver was examined microscopically) ([redacted] "Letter Report" dated [redacted]).

In a 6-week oral (gavage) study in Beagle dog (0, 200, 1000, 2000 mg/kg/day; [redacted] Final Report, [redacted]), the only clear drug-related finding reported by [redacted] was fecal changes (including liquid, mucoid) at the MD and HD. (No Agency review of this study could be found; stated to be GLP compliant by [redacted])

Reproductive and developmental toxicity: In an embryo-fetal development study in pregnant Wistar rat administered a [redacted] combination of [redacted] on GD 6-16, no adverse effects on fetal development were observed at a dose of 1000 mg/kg (separate control group was included) ([redacted] final report dated [redacted]).

Genotoxicity: The genotoxic potential of [redacted] was tested in an *in vitro* Ames assay using *S. typhimurium* tester strains TA98, TA100, TA1535, TA1537, and TA1538, apparently at a single concentration (2000 µg/plate) [redacted] for Mutagenicity Testing, final report dated [redacted]). The study was reported as negative, both in the absence and presence of metabolic activation.

[redacted] was reported to be negative in an *in vitro* mouse lymphoma *tk* assay at concentrations up to "880 µg/plate" ([redacted]), in the absence and presence of metabolic activation ([redacted] final report dated [redacted]; stated to be GLP compliant by [redacted]).

[redacted] was reported to be negative in an *in vivo* mouse micronucleus assay at acute oral doses "up to 2000 mg/kg" ([redacted] final report dated [redacted]).

[redacted]

Absorption: the absorption of [redacted] was not evaluated.

Toxicity: no acute toxicity studies of [redacted] were conducted.

A 6-month (+ 4-week recovery) oral (gavage) toxicity study was conducted in Wistar rat (10/sex/group) at doses of 0, 200, 600, and 1500 mg/kg/day (Project No. 3-4-242-84, [redacted]; signed QA statement; signed study report [although title page states that this is a "Provisional Report"]; stated to be GLP compliant; study report available). The primary drug-related findings consisted of increases in liver weight (all doses in males, and in MDF and HDF), correlated with microscopic evidence of hepatocyte peripheral fatty degeneration at the HD, and "activation" of the thyroid epithelium at all doses in main-study animals and in treated males at the end of the recovery period. The incidence and severity of the thyroid findings are summarized in the following table (doses are in mg/kg/day):

STAGE	MALES				FEMALES			
	0	200	600	1500	0	200	600	1500
MAIN STUDY								
1	2	--	--	--	10	7	1	--
2	3	--	--	--	--	--	--	--
3	5	3	--	--	--	3	9	6
4	--	5	1	3	--	--	--	4
5	--	2	9	7	--	--	--	--
RECOVERY								
1	--			--	8			--
2	2			1	2			7
3	8			4	--			3
4	--			5	--			--
5	--			--	--			--

Stage 1: normal, flat-ellipsoid nuclei; Stage 2: normal, but ellipsoid, slightly rounded nuclei; Stage 3: slight activation, Stage 4: definite activation; Stage 5: extensive activation.

According to the "expert report" ([redacted]):

> "The semiquantitative evaluation of the thyroid structures (follicle diameter, epithelial height, nucleus size and nuclear stainability) definitely indicate the tendency towards an activation of the thyroideal *[sic]* epithelium especially in the male animals of the test groups."

Similar thyroid changes were evident in recovery animals, although of lesser severity; liver findings were not evident at the end of the recovery period.

Apparently because of the thyroid findings observed in this study, additional nonclinical studies were conducted for [redacted]:

- In a 6-week oral toxicity study in male NMRI mice (12/group) [redacted] final report dated [redacted]; QA statement but no signed GLP compliance statement), [redacted] was administered orally (gavage) at doses of 0, 100, 600, and 1500 mg/kg/day. Only thyroid gland was examined histologically. "A clear indication of thyroid activation" was observed at the HD, with "A slight tendency toward activation" at the MD. Thyroid changes were characterized by "epithelial hyperplasia and hypertrophy, and irregularity in size of follicles." The LD was the NOAEL for thyroid effects.
- In a 6-week oral toxicity study in New Zealand White rabbit (6/sex/group) ([redacted] final report dated [redacted]; QA statement but no signed GLP compliance

statement), [redacted] was administered orally (gavage) at doses of 0, 100, 600, and 1500 mg/kg/day. Only thyroid gland was examined histologically. Thyroid activation was detected at the MD ("slight") and HD ("a clear indication"). The LD was the NOAEL for thyroid effects.

- In a repeat 6-month oral toxicity study in Wistar rat (15/sex/group) (Project No. [redacted] final report dated [redacted]; signed GLP statement indicates "To the best of my knowledge this study was conducted in compliance with the Good Laboratory Practice Regulations…as specified by the U.S. Food and Drug Administration…"; study report available), [redacted] was administered at oral (gavage) doses of 0, 10, 30, and 100 mg/kg/day. Only thyroid gland was examined histologically. According to the signed pathology report [redacted], no drug-related microscopic changes in thyroid gland were detected.

Reproductive and developmental toxicity: a combination of [redacted] was tested in an embryo-fetal development study in pregnant Wistar rat (*see under* [redacted]).

Genotoxicity: [redacted] was negative in an *in vitro* Ames assay conducted using *S. typhimurium* tester strains TA98, TA100, TA1535, TA1537, and TA1538 at 3000 µg/plate, with and without metabolic activation.

Summary and Conclusions

None of the excipients in the TBM formulation of IPX066 are novel; all are in numerous previously approved drug products. However, the specification limits for four excipients in the TBM formulation of IPX066 would result in total daily doses that exceed the unit amounts (or "maximum potency") specified in the Inactive Ingredients Database (IID). Two of these, triethyl citrate and [redacted]tartaric acid, are endogenous compounds and confirmed as GRAS by FDA. Whereas the maximum daily dose of triethyl citrate [redacted] is within the daily amount [redacted] consistent with the GRAS designation, that of [redacted]tartaric acid [redacted] substantially exceeds the daily amount [redacted] discussed in the SCOGS opinion. (No approved product could be identified that provides a similar daily dose of [redacted]tartaric acid; two drug product [approved in 1999 and 2010] provide daily doses of up to [redacted] of tartaric acid.) However, the SCOGS opinion notes that doses of up to 2.3 gm/kg/day for 150 days in rabbit and 1.2 gm/kg/day for 2 years in rat resulted in no notable toxicity, and a review conducted by [redacted] specified acceptable daily doses of up to 30 mg/kg/day for tartaric acid. [redacted] reported the results of a study in which CFY rats ("a hysterectomy-derived strain of Sprague-Dawley origin") were administered monosodium [redacted]tartrate in the diet at doses (of tartaric acid) up to 2.46-3.20 g/kg/day for 2 years. Findings included dose-related decreases in mortality rate and body weight (relative to controls). Body weight effects were attributed to the 2.56% decrease in nutritional content of the treated diet(s), and may have influenced the mortality rate. No adverse effects on clinical observations, clinical pathology, or histopathology were noted. Based on the available information, the specification limits for triethyl citrate and [redacted]tartaric acid do not raise a safety concern.

To support the specification limits for the other two excipients, [redacted], that exceed (based on total daily dose) the unit amounts specified in the IID, the sponsor provided an LoA to DMF [redacted]) and a summary evaluation by [redacted]

(b) (4)). Of the DMF studies described by (b) (4), only the study reports for the two 6-month oral toxicity studies of (b) (4) in Wistar rat were reviewed in detail by Dr. McKinney; however, most of the nonclinical studies in DMF (b) (4) have been reviewed by multiple divisions (under LoAs from (b) (4)) to support other NDA applications. As noted by the sponsor, the per capsule amounts of (b) (4) fall below the maximum amounts in an approved drug product (i.e., (b) (4) for (b) (4) and (b) (4) respectively), but the total daily dose of each at the anticipated maximum human daily dose (b) (4) and (b) (4), respectively) exceeds the unit amounts. Although the maximum unit amount of (b) (4) is close to the total daily dose of (b) (4) from IPX066, this "per form" limit is only for a product intended for short-term [10 day] use. However, there are other products approved (1996 and 2009) for chronic use that at the maximum human daily dose would result in a dose of (b) (4) slightly lower than that for IPX066 (i.e., (b) (4) No excipient-related safety issues have been identified with either product; therefore, the amount of (b) (4) in IPX066 is acceptable. No approved product could be identified that would support the daily dose of (b) (4) at the maximum recommended daily dose of IPX066.

DMF (b) (4) does not provide a full nonclinical assessment for either (b) (4); however, it would be reasonable to accept less than that for these excipients because systemic exposure would be expected to be relatively low, considering their molecular weight (average of (b) (4) Oral absorption was assessed only for (b) (4) but was demonstrated to be low. Since (b) (4) differ only in the ratio (b) (4) respectively) of the same two monomers (b) (4), it might be expected that oral absorption would also be relatively low for (b) (4). However, clear systemic effects were observed with (b) (4) in multiple species, so some extent of systemic exposure to excipient-related material must be assumed.

Based on the available data, the primary toxicity is thyroid "activation", observed in multiple species (mouse, rat, rabbit) with (b) (4). (Thyroid activation was not detected in 30-day and 6-week oral toxicity studies of (b) (4) in rat and dog, respectively, at doses up to 2000 mg/kg/day.) The NOAEL for thyroid activation in mouse, rat, and rabbit was 100 mg/kg/day, although chronic administration was assessed only in rat. Using the most sensitive species (mouse), this NOAEL provides no safety margin, on a body surface area (mg/m^2) basis, compared to the anticipated maximum total daily dose of (b) (4) from IPX066. According to (b) (4)), the safety margin is (b) (4) for (b) (4), based on mg/kg and (b) (4) capsules per day; however, based on the MHDD of (b) (4) capsules per day, the safety margin on a mg/kg basis is (b) (4). The sponsor notes that interspecies comparisons based on body weight (mg/kg) are "…the appropriate comparator for an inactive ingredient." The 100 mg/kg dose was the NOAEL in all species tested, which is one basis for use of mg/kg; however, the available data are not sufficient to conclude that a dose of 100 mg/kg/day would remain an NOAEL in mouse or rabbit with chronic administration. Also, the thyroid findings would suggest systemic, not local, effects; therefore, body surface area comparisons appear the more appropriate. In addition, due to the high molecular weight of (b) (4), systemic toxicity is unexpected and would argue for a more thorough assessment of toxicity, e.g., a chronic toxicity study in non-rodent.

Conclusions

The data provided by the sponsor do not adequately support the safety of the daily dose of the excipient (b) (4), at the MHDD of IPX066. The sponsor was asked to provide additional information on the safety of (b) (4), particularly addressing concerns regarding the thyroid effects observed in multiple species. (It should be noted that the oral toxicity studies of

(b) (4) in rat were not sufficient, by design, to determine if thyroid gland is a target organ; acceptability of the total daily dose for this excipient is based solely on prior approval of drug products for chronic use that result in comparable total daily doses of (b) (4).)

Information provided by the sponsor by email (9/27/2012) and to the NDA (SDN 26, 10/2/2012) was determined to constitute a major amendment (Agency letter, dated 10/4/2012), extending the PUDFA deadline by three months. Whether or not this additional information adequately addresses concerns regarding the safety of (b) (4) at the MHDD of IPX066 will be addressed in a separate memo.

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/s/

LOIS M FREED
12/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	203-312
Supporting documents:	SDN 1
Applicant's letter date:	DEC 21, 2011
CDER stamp date:	DEC 21, 2011
Product:	IMPX066 (Rytary©)
Indication:	(b) (4) Parkinson's disease (b) (4), post-encephalitic parkinsonism, and (b) (4) parkinsonism following carbon monoxide (b) (4) or manganese intoxication.
Applicant:	Impax Laboratories, Inc
Review Division:	DNP
Reviewer:	LuAnn McKinney, D.V.M.
Supervisor/Team Leader:	Lois M. Freed, Ph.D.
Division Director:	Russell Katz, M.D.
Project Manager:	Tracy Peters, Pharm.D.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 213-312 are owned by Impax Laboratories, Inc. or are data for which Impax Laboratories has obtained a written right of reference. Any information or data necessary for approval of NDA 203-312 that Impax Laboratories, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are for descriptive purposes only and are not relied upon for approval of NDA 203-312

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1 Executive Summary

1.1 Introduction

The NDA for IPX066 (Rytary©) was submitted by IMPAX Laboratories, Inc., Hayward, CA, on 12/21/2011, as a 505(b)(2) application relying on the prior finding of safety and efficacy for Sinemet CR (NDA 19-856), Sinemet (NDA 17-555), and Stalevo (NDA 21-485).

IPX066 (Rytary©) is an extended release formulation of two forms of enteric-coated (b) (4) of Carbidopa (CD) and Levodopa (LD) for the treatment of Parkinson's disease. The sponsor submitted an LOA dated 12/18/2008 to Drug Master File (b) (4) for the excipient enteric coatings, (b) (4), and a report summarizing 23 nonclinical studies.

No new nonclinical pharmacokinetics studies were performed by the sponsor; a review of the recent published data established there are no new relevant findings regarding the pharmacokinetics of Levodopa or Carbidopa that would impact the labeling for IPX066.

1.2 Brief Discussion of Nonclinical Findings

The maximum recommended human dose (MRHD) of Carbidopa and Levodopa fall within the approved MRHD of the RLD: the per capsule ratio of CD:LD is 1:4 in 4 strengths: 23.75-95 mg, 36.25-145 mg, 48.75-195 mg, and 61.25-245 mg (CD-LD). Single capsules of IPX066 (Rytary©) contain (b) (4) mg (b) (4) and (b) (4) mg (b) (4) in the highest strength capsules. These amounts fall within those levels per oral dose unit in currently approved drugs, per the Inactive Ingredient Search for Approved Drug Products.

(b) (4) are co-polymers of (b) (4) and the metabolite (b) (4), and are constituents of the enteric coating of IPX066. They dissolve at different pH levels allowing controlled release of encapsulated drugs at different levels of the intestine. The sponsor submitted an LOA dated 12/18/2008 to the Drug Master File (b) (4) for (b) (4) and a report summarizing 23 nonclinical studies including genotoxicity, reproductive, developmental, and single- and repeat-dose oral toxicity studies of (b) (4).

At a MRHD per day of 612.5-2450 mg (CD-LD) from IPX066 (Rytary©), patient exposure to (b) (4) will be (b) (4) mg/day and to (b) (4) will be (b) (4) mg/day. These amounts exceed FDA IIG listed maximal unit potencies. However, the daily MRHD of (b) (4) in IPX066 is less than drugs listed in the IIG and the proposed total daily dose of (b) (4) is (b) (4) fold below the HED of the NOEL/NOAEL of a pivotal toxicology study.

1.3 Recommendations

1.3.1 Approvability

IPX066 (Rytary ©) does not exceed carbidopa (CD) and levodopa (LD) plasma exposures achieved with marketed CD/LD products. Therefore, no additional nonclinical studies are needed to support approval of the drug substance.

The levels of excipients, [redacted] (b) (4), are not found to be of toxicologic concern.

1.3.3 Labeling: There are no new relevant findings regarding the pharmacokinetics of Levodopa or Carbidopa that would impact the labeling for IPX066.

2 Drug Information

2.1 Drug

Generic Name: Carbidopa + Levodopa

Chemical Name:
CD- (S)-α-hydrazino-3,4-dihydroxy-α-methylbenzenepropionic acid
LD- monohydrate and (−)-(3,4-dihydroxyphenyl)-L-alanine

Molecular Formula/Molecular Weight:
CD- $C_{10}H_{14}N_2O_4.H_2O$ MW: 244.25
LD- $C_9H_{11}NO_4$ MW: 197.19

Pharmacologic Class:
CD- Decarboxlyase inhibitor
LD- Amino acid

2.2 Relevant NDAs/DMF:

Sinemet CR (NDA 19-856)
Sinemet (NDA 17-555)
Stalevo (NDA 21-485).
[redacted] (b) (4)

2.3 Drug Formulation

IPX066 (Rytary©) is an extended release formulation of two forms of enteric-coated [redacted] (b) (4) of Carbidopa (CD) and Levodopa (LD). The enteric coatings [redacted] (b) (4) dissolve at different pH levels allowing controlled release at different levels of the intestine.

At a per capsule ratio of 1:4, the MRHD of Carbidopa and Levodopa fall within the approved MRHD of the RLD.

2.4 Comments on Excipients:

There are no novel excipients. Single capsules of IPX066 (Rytary©) contain (b) (4) in the highest strength capsules.

Sponsor's table of excipients, to include maximum potency in the IIG:

Table 1: Inactive Ingredients Present in IPX066

Ingredient	Composition (w/w%)	Amount in IPX066 at 245 mg LD dose strength (mg/capsule)	Maximum Potency in IIG (mg)	Intake from IPX066 (mg/day)[a]
Croscarmellose sodium	(b) (4)			
Ethyl cellulose				
Hypromellose (b) (4)				
(b) (4) tartaric acid				
Magnesium stearate				
Mannitol				
Methacrylic acid copolymer (b) (4)				
Methacrylic acid copolymer (b) (4)				
Microcrystalline cellulose				
Povidone				
Sodium starch glycolate				
Sodium lauryl sulfate				
Talc				
Triethyl citrate				

a Estimated for a maximum human daily dose of 612.5-2450 mg of CD-LD from IPX066 (10 capsules of 61.25-245 mg).
Abbreviations: LD = levodopa; IIG = FDA Inactive Ingredients Database.

At 10 capsules of 61.25/245 mg, patient exposure to (b) (4) will be (b) (4) mg/day, to (b) (4) will be (b) (4) mg/day and to (b) (4) tartaric acid will be (b) (4) mg/day. The daily dose of (b) (4) tartaric acid would be (b) (4) fold that found in approved drugs. (b) (4) tartaric acid is also a direct food additive. The sponsor cites the 21CFR184.1099; Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives. In a two-year bioassay in the rat, the Human Equivalent Dose (HED) of the NOAEL is (b) (4)). The oral route of exposure and general low level of toxicity allow the daily level of exposure in Rytary© to be acceptable.

The total daily dose of [redacted] in approved drugs containing [redacted] exceeds the MRHD total daily dose of Rytary© by [redacted] fold. The approved drugs are to be administered for 10 days to 2 weeks, and Rytary© administration would be chronic. The molecule is of a sufficient size to preclude absorption and lack of absorption is supported by negative results in an absorption study of orally administered [redacted] labeled [redacted] in the DMF. Further, no systemic effects from [redacted] are seen in rats and dogs at the Maximal Feasible Doses in 2- and 4-week toxicity studies in the DMF. The lack of absorption of the compound and the absence of systemic effects make the level of [redacted] in IPX066 (Rytary ©) to be not of toxicologic concern.

In drugs containing [redacted], the MRHD yields a total daily dose less than that in IPX0066 (Rytary ©). However, the total daily dose of [redacted] in the IPX066 (Rytary©) exceeds products containing [redacted], approved for regimens up to 6 weeks, by [redacted] fold.

Table: [redacted] level comparisons with Inert Ingredients Guide (IIG)

	[redacted] (60 kg human)			[redacted] (60 kg human)		
	mg	Mg/kg	Mg/m2	mg	Mg/kg	Mg/m2
Single capsule	[redacted]					
IIG						
MRDD IPX066						
MRDD IIG						
IPX066 vs. IIG (MRDD)						
	Within limits			Exceeds limits		

2.6 Proposed Clinical Population and Dosing Regimen:

The maximum recommended daily dose (MRDD) of IPX066 (Rytary ©) is 612.5-2450 mg (CD-LD) from IPX066 (Rytary©).

3 Studies Submitted

No studies of the parent compound were submitted. As a 505 (b)(2), the application relies on the finding of safety and efficacy for approved NDAs 19-856, 17-555, and 21-485.

3.1 The sponsor submitted an LOA dated 12/18/2008 to the Drug Master File [redacted] (for the [redacted] excipients) and a report: [redacted] The report summarized 23 nonclinical studies

and did not assess the studies for validity, integrity, or quality of the data. As such, the summary offers only an informed opinion.

(b) (4)

(b) (4)

Upon review of amendments to DMF (b) (4), both polymers are not genotoxic by the Ames mutagenicity test (DMF (b) (4) Ch 9.0, Amended (b) (4) In a pilot dosing (LD_{50}) study of (b) (4) (DMF (b) (4) Ch 10.10) in dogs, effects were limited to softened stools and there were no adverse effects at the oral HD of 10g/kg.

Studies Reviewed

This review addresses the safety of the proposed MRHD total dose of (b) (4).

A provisional, but QA audited, report "carried out in accordance with the principles" of GLP, (b) (4) The 6-month study of rats dosed at the highest dose levels in a chronic study and, given the chronicity of IPX066 (Rytary©) therapy, this 6-month study is considered pivotal.

A follow-on target-organ study (b) (4) was conducted at lower dose levels to establish a NOAEL or NOEL.

4 General Toxicology

4.2 Repeat-Dose Toxicity

Study title: Six Month Toxicity Study on [redacted] by Oral Administration to Rats (Followed by a 4-Weeks Recovery Period)

Study no.:	N/A
Study report location:	DMF [redacted] Chapter 9.16 of DMF [redacted] (Amendment [redacted]
Conducting laboratory and location:	[redacted]
Date of study initiation:	[redacted]
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	[redacted] Batch 8003/26, [redacted] %

Key Study Findings: Adverse thyroid epithelial changes were seen at LDM, MDM, HDM, in recovery HDM, and in HDF.

Methods

Doses:	0, 200, 600, 1500 mg/kg
Frequency of dosing:	daily
Route of administration:	Oral gavage
Dose volume:	10 mL
Formulation/Vehicle:	Deionized water
Species/Strain:	Wistar (BOR:WISW)
Number/Sex/Group:	25
Age:	6 weeks
Weight:	M:97-128 g F: 87-123 g
Satellite groups:	10/sex C and HD recovery for 4 weeks post-dose.
Unique study design:	Full Histology-10/sex C and HD. Thyroid and Sudan III stained frozen liver 10/sex all groups
Deviation from study protocol:	Water filtration methods changed week 9-10.

Observations and Results

Mortality:

Table: Mortality in a 6-month [redacted] Toxicity study.

Group	Dose	M	F:	Cause:
C	Vehicle (water)	1	2	Pneumonia(M), Nephritis and calculi(F), Gavage error (F)
I	200 mg/kg	2	2	Post-bleed (M,F), Pneumonia (M), Pulmonary congestion (F)
II	600 mg/kg	2	1	Pneumonia (F), Hemothorax (M), Pneumonia (M)
III	1500 mg/kg	2	0	Pneumonia (M and M)

Mortality in 7 rats was attributed to pneumonia and 5 of the 7 died or were euthanized during Study Week 12. The relationship of the morbidity to the reduced water intake and body weight loss in Study Weeks 10-11 is not discussed; however, those rats had reduced food consumption (up to 30% of baseline) in Study Weeks 10-12.

Clinical Signs: No difference between groups.

A change in the water filtration system and subsequent palatability resulted in a transient drop in food consumption and body weights in all groups from Weeks 10 to 11.

Body Weights: No difference between groups

Feed Consumption: No difference between groups.

Hematology: No difference between groups, within limits of normal for the laboratory.

Clinical Chemistry: No difference between groups, within limits of normal for the laboratory.

Urinalysis: No difference between groups, within limits of normal for the laboratory.

Gross Pathology: At necropsy, there were no significant differences between groups and no macroscopic dose-related changes were observed.

Organ Weights: There was no difference between groups.

Histopathology:

Adequate Battery: 10/sex Vehicle Control and 10/Sex HD- Yes.

Paraffin-embedded thyroid glands and Sudan-III stained frozen liver sections were examined microscopically from 10 per sex per group of main study and recovery rats. A full battery of paraffin-embedded tissues was examined microscopically from 10 CM, 10 CF, 10 HDM, and 10 HDF from the main study.

Peer Review: No

Histological Findings:

Histologically, various inflammatory changes, to include non-suppurative tracheitis, interstitial pneumonia, hepatic lymphocytosis, hydrometra, testicular degeneration, mild

chronic progressive nephropathy, and one case of intestinal parasites, were diagnosed in C and HD animals. There was no dose-relationship.

The pathologist noted that "The inflammatory changes in the different organs are the expression and effect of inapparent [sic] infections. These findings can nearly always be observed in rats". The presence of grossly observed pneumonia, often with enlarged "sternal" lymph nodes, in rats that were moribund or found dead is likely due to endemic mycoplasmosis, an infection in laboratory rats that is less common under current (2012) laboratory conditions.

Special Evaluation:

Hepatic lipidosis ("fatty change", confirmed by Sudan III staining), was increased in incidence and severity in the HDM and HDF; there was no difference in incidence or severity between sexes. Individual hepatocyte fatty change was seen in control and HDM and HDF from both the main study and recovery animals. Slight to moderate fatty degeneration of peripheral (interpreted as periportal) hepatocytes was limited to rats from the main study: one CF, 2 MDM, 5 HDM, and 4 HDF. The pathologist attributed the fatty change to "metabolic stress." The change was not seen upon recovery, and mild hepatocellular lipidosis is not considered to be adverse.

Thyroid epithelial changes were staged from 1 to 5 (see table). The terminology is non-standard; however, it is descriptively compatible with epithelial hypertrophy and hyperplasia ("pad formation"). The presence of small (micro) follicles is compatible with increased thyroglobulin release.

Table of staging criteria for thyroid epithelial changes in a 6-month (b) (4) Toxicity study

Stage	Thyroid epithelial changes
1	No change (within limits of normal)
2	Slight increase in nuclear size, and basophilia, some low-cuboidal.
3*	As 2, plus central follicles smaller, with pale-staining enlarge nuclei and cuboidal epithelium
4**	Diffuse low-cuboidal epithelium, large pale nuclei and central micro-follicles (reduced colloid)
5***	Diffusely cuboidal epithelium, "pad formation", microfollicles seen both centrally and peripherally

* Considered to be evidence of slight "activation"
** Considered to be evidence of "definite activation"
*** Considered to be evidence of "extensive activation"

Stages 1-3 are considered to be within limits of normal physiology; thyroid changes in all CM ranged from normal to 3 and in all CF from normal to 2.

Thyroid changes in LDF and MDF and recovery HDF are not significantly different from controls; however, 4/10 HDF from the main study were found to have stage 4 changes.

Stages 4 and 5 were seen in 7/10 LDM, all MDM, and all HDM from the main study and 5/10 recovery HDM.

Thyroid changes were indistinguishable from controls and within limits of normal in both LDF (Thus, a NOEL [200 mg/kg] is found only in female rats.)

The thyroid changes are directly attributed to [redacted]. Advanced diffuse change was seen in LDM, MDM, HDF, and HDM and in 4/10 HDM 4 weeks after cessation of the drug. Further, there was clinical evidence of hyperactivity and piloerection in the HD animals. Under the conditions of this study, the changes, although without significant systemic effects, are considered to be adverse and the NOAEL and NOEL are less than 200 mg/kg by oral gavage of [redacted].

Study title:	[redacted]
Study no.:	n/a
Study report location:	DMF [redacted]
Conducting laboratory and location:	[redacted]
Date of study initiation:	[redacted]
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	[redacted], Batch 8003/26, [redacted]%

Key Study Findings:

This is a follow-on study to a 6-month rat study in which clinical signs and histologic changes were seen in thyroid glands at higher dose levels.

In this study, in-life observations, hematologic data, and macroscopic observations were indistinguishable between groups.

Histologic examination was limited to the thyroid glands. Dose-related histologic change, seen in LDM, MDM, and HDM, consisted of a reduction in the incidence of "elevated thyroid epithelium" when compared to CM, CF, LDF, MDF, and HDF. The change is not adverse and the NOAEL for thyroid histologic changes is at the high dose of [redacted] mg/kg/day. The NOEL is less than [redacted] mg/kg/day.

Methods

Doses:	0, 10, 30, 100 mg/kg
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	% w/v Deionized water , prepared daily
Species/Strain:	Wistar Rats (BOR:WISW)
Number/Sex/Group:	15
Age:	6 weeks
Weight:	132-169 g (M); 111-142 g (F)
Satellite groups:	None
Unique study design:	Histology limited to thyroid glands (L and R)
Deviation from study protocol:	One death attributed to intra-tracheal gavage

Observations and Results

Mortality: 1 LDF, (Study Week 15) died post-dose- attributed to intra-tracheal gavage.

Clinical Signs: Daily observations and Noise sensitivity and Modified IRWIN screen – Study Weeks 0, 13, 26: No difference between groups

Body Weights: Weekly- No difference between groups

Food Consumption: Weekly- No difference between groups

Ophthalmoscopy: Study Weeks 0, 13, 26: No difference between groups

Hematology: Study Weeks 0, 13, 26: No difference between groups

Gross Pathology: No test article related lesions were observed. Individual instances of hydrometra, cervical cysts, cryptorchid testes, and hydronephrosis were seen across all test groups.

Organ Weights: Tracheal segment with thyroids, L and R thyroid glands, and liver: No difference between groups.

Histopathology

Kidney, pancreas, testes with epididymes and a sample of liver were immersion-fixed in Bouin's solution. The remainder of a standard battery, to include liver, was fixed in 10% formalin.

Histologic exam was limited to thyroid glands of 10/sex/group.

Histological Findings: Changes of "elevation of thyroid epithelium" were observed in all groups. Seen at 60% and 50% in individually examined thyroid glands of CM, and 10% of CF, the change was reduced to as low as 10% incidence (per thyroid gland) in LDM,

MDM, and HDM. The incidence remained at 10% per gland in all F. Incidental follicular cysts were seen in all groups and no differences were noted between groups.

Sponsor's Table: Incidence of epithelial changes in the thyroid glands of male rats

Project Summary Table
SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 120-89 FATES: Terminal sacrificeSEX: MALE

GROUP:		I		II		III		IV	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
Thyroid I	# Ex	10		10		10		10	
Elevation of thyroid epithel		5	(50)	3	(30)	2	(20)	1	(10)
Follicular cyst		0	(0)	1	(10)	0	(0)	1	(10)
Thyroid II	# Ex	10		10		10		10	
Elevation of thyroid epithel		6	(60)	1	(10)	1	(10)	2	(20)
Follicular cyst		0	(0)	1	(10)	0	(0)	0	(0)

Sponsor's Table: Incidence of epithelial changes in the thyroid glands of female rats

Project Summary Table
SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 120-89 FATES: Terminal sacrificeSEX: FEMALE

GROUP:		I		II		III		IV	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
Thyroid I	# Ex	10		10		10		10	
Elevation of thyroid epithel		1	(10)	0	(0)	0	(0)	1	(10)
Follicular cyst		1	(10)	0	(0)	0	(0)	0	(0)
Autolysis		0	(0)	1	(10)	0	(0)	0	(0)
Thyroid II	# Ex	10		10		10		10	
Elevation of thyroid epithel		0	(0)	0	(0)	0	(0)	1	(10)
Autolysis		0	(0)	1	(10)	0	(0)	0	(0)

5 Integrated Summary and Safety Evaluation

The NDA for IPX066 (Rytary©) is a 505 (b) (2) application. The drug substance is within specifications for the RLDs and no further nonclinical testing is necessary.

The drug product is an extended release formulation of enteric-coated (b) (4) of Carbidopa (CD) and Levodopa (LD) and tartaric acid. All excipients are within the limits of the IIG on a per capsule basis. However, at the maximum recommended daily dose these excipients exceed FDA IIG listed unit potencies.

(b) (4) tartaric acid is recognized as GRAS as a direct food additive. In a two-year bioassay in the rat, the Human Equivalent Dose (HED) of the NOAEL was (b) (4). The oral route of exposure and general low level of toxicity allow the daily level of exposure in Rytary © to be acceptable.

The daily dose of (b) (4) in approved oral drugs is greater than the amount in the daily maximal dose of IPX066 (Rytary©) and, in the absence of evidence of absorption or systemic effects from oral administration of the excipient, the levels of (b) (4) in IPX066 (Rytary©) are not of toxicologic concern.

The total daily dose of (b) (4) in the IPX066 (Rytary©) exceeds that of approved oral drugs by (b) (4) fold.

In justification of the (b) (4) levels, the sponsor submitted an LOA to the Drug Master File and a report that summarizes 23 nonclinical studies and concludes:

> "(b) (4) are high molecular weight copolymers which are not absorbed, consistent with the very low potential for acute oral toxicity. The NOAEL for rats with repeated oral dosing for up to 6 months was (b) (4) mg/kg/day and for dogs with 6 weeks dosing was (b) (4) mg/kg/day.
>
> "The nonclinical safety database on (b) (4) would indicate a low potential for toxicity at the proposed use levels in IPX066. In the absence of any meaningful oral absorption of (b) (4) (and (b) (4)), safety factors based on animal/human using mg/kg/day is the appropriate comparator for an inactive ingredient. At the MHRDD, these margins would be (b) (4) for (b) (4) and (b) (4)."

The report does not assess the studies for validity, integrity or quality of the data and, as such, the summary offers only an informed opinion.

A provisional report "carried out in accordance with the principles" of GLP, "Six Month Toxicity Study on (b) (4) by Oral Administration to Rats (Followed by a 4-Weeks Recovery Period) has been cited in a nonclinical review of an

approved drug containing (b) (4) and, given the chronicity of Parkinson's disease therapy, the 6 month study was reviewed for this application.

Dose-related slight to moderate fatty degeneration of peripheral (interpreted as periportal) hepatocytes was seen in rats from the main study: one CF, 2 MDM and 5 HDM and 4 HDF. The pathologist attributed the fatty change to "metabolic stress". The change was not seen upon recovery, and mild hepatocellular lipidosis is not considered to be adverse.

Histologic evidence of hyperthyroidism was found in 4/10 HDF from the main study, and 7/10 LDM, all MDM, all HDM from the main study, and 5/10 recovery HDM. Clinically, piloerection and hyperactivity were observed in all HD animals.

In rats, especially males, thyroid hypertrophy and hyperplasia with reduction in stored colloid are often compensatory to metabolic activation of liver enzymes that reduce circulating thyroglobulin levels and modest changes are not considered to be adverse. Although thyroglobulin levels were not assessed and the hematology and clinical chemistry values were the same between groups, the pathologist referred to the glands as functionally "hypothyreotic", interpreted to mean reduced levels of thyroglobulin.

The hepatic and thyroid changes may be attributable to stress of oral gavage with an inert compound, rather than pharmacologically induced; however, neither food consumption nor hematologic values evidence significant stress and no changes were noted in HE and Sudan III stained adrenal glands. The thyroid epithelial changes, although mild, are considered to be dose-related. There is no evidence of centrilobular hepatocellular hypertrophy (as seen with hepatic enzyme activation); thus, the thyroid changes are directly attributed to (b) (4).

Under the conditions of this study, the thyroid changes are considered to be adverse and the NOAEL and NOEL in this 6-month study are less than (b) (4)

A follow-on 6-month study, with lower dose levels and histologic examination limited to the thyroid glands, was performed at the same facility. Clinical signs and hematologic values were the same within all groups. A reduction in the 50-60% incidence of "elevated thyroid epithelium" in glands of CM is a dose-related effect in LDM, MDM, and HDM. The histomorphology of thyroid glands of female rats is indistinguishable from vehicle CF. The histologic change of "elevation of thyroid epithelium" is morphologically analogous to the "stage 2" in the first 6-month rat study and is considered to be within limits of normal. There is no evidence of systemic effects of the elevated epithelium in CM and the reduced incidence in male rats is not considered adverse. The NOAEL of chronically administered oral (b) (4)

Although the [redacted] levels in the daily MRHD of IMPX066 exceed that of current IIG by [redacted] fold, the proposed total daily dose of [redacted] fold below the HED (at the NOAEL) of [redacted] for 6 months, on a mg/kg basis.

Conclusion: The daily levels of [redacted] are less than that of approved drugs and the levels of [redacted] are [redacted] fold less than the no adverse effect level.

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/s/

LUANN MCKINNEY
09/25/2012
re-submitted/replaced

LOIS M FREED
09/26/2012
Please see memo for comments.